The American Journal of Medicine

December 1948

THE YORKE PUBLISHING COMPANY, INC.
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The American Journal of Medicine

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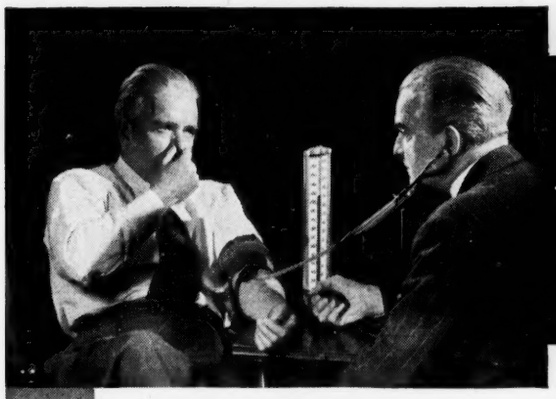

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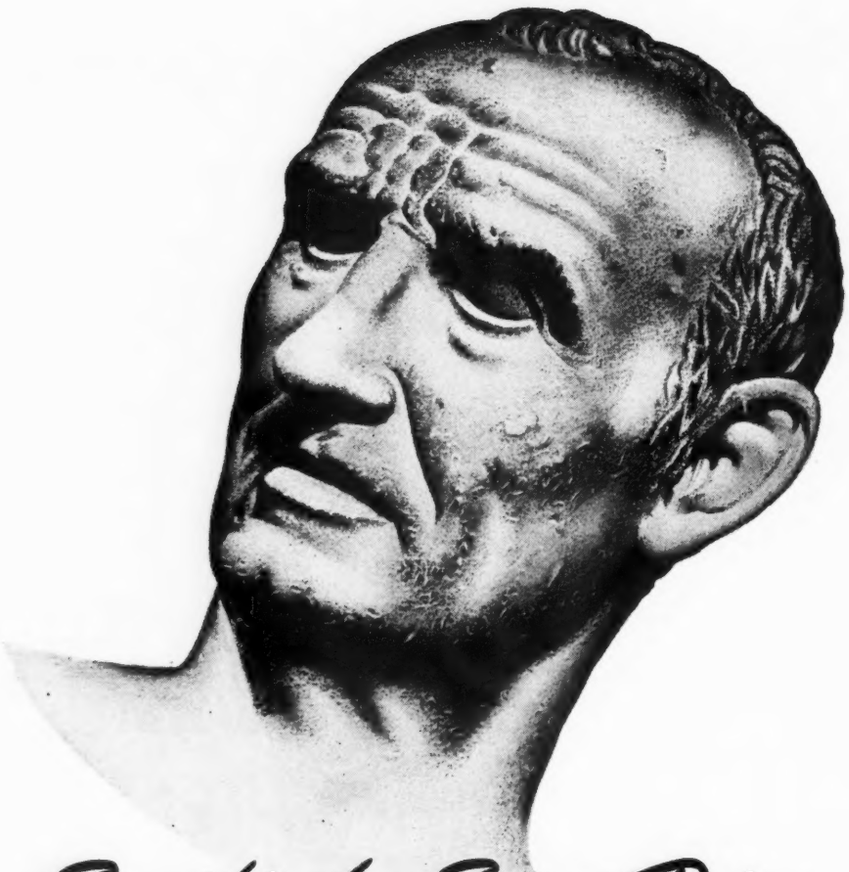
FIRST OF A SERIES

BREATH-HOLDING TEST:[1-2] With the patient sitting in a quiet room, the blood pressure is determined at five minute intervals until a basal level is obtained. This usually takes from twenty to forty-five minutes. The test procedure is explained to the patient, followed by another brief rest period until the basal level is again reached.

At an observed moment of normal quiet expiration the patient is instructed to compress both nostrils suddenly and simultaneously to close the mouth by compressing the lips. The breath is held for twenty seconds during which the systolic rise is determined. Following a rest period and return to the basal level, the same test is repeated in order to determine the diastolic rise. (Normal systolic or diastolic rise does not exceed 22 mm.)

SIGNIFICANCE: Holding the breath in normal expiration increases the carbon dioxide content of the alveolar air. This is quickly reflected in the blood with stimulation of the vasomotor center and a resulting rise in the blood pressure. In hypertensive patients the rise in pressure is from two to four times greater than in normal subjects.

1. Ayman, David, and Goldshine, Archie D.: *Arch. Int. Med.*, 63:899, May, 1939.
2. Feldt, Robert H., and Wenstrand, D. E. W.: *Arch. Int. Med.*, 67:1157, June, 1941.



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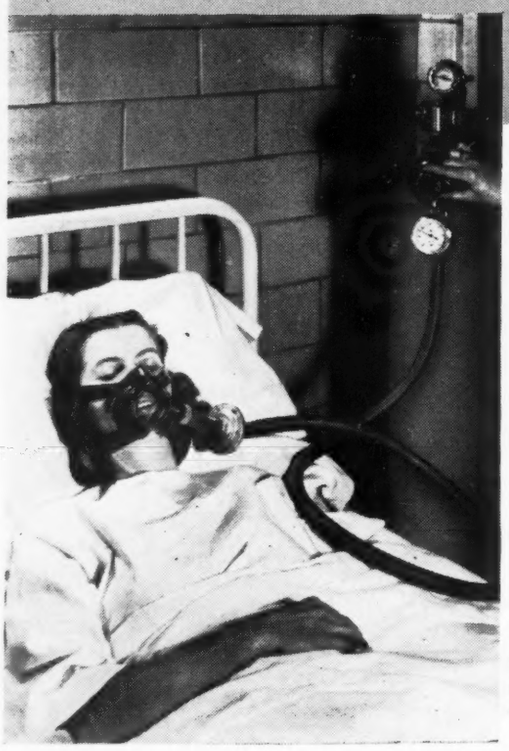
A NEW DEVELOPMENT

in the treatment of pulmonary disorders with

INTERMITTENT POSITIVE PRESSURE



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Clinico-pathologic Conference

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General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

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BANCROFT, F. W., STANLEY-BROWN, M. and QUICK, A. J. Postoperative thrombosis and embolism. *Am J. Surg.*, 26: 648, 1945.

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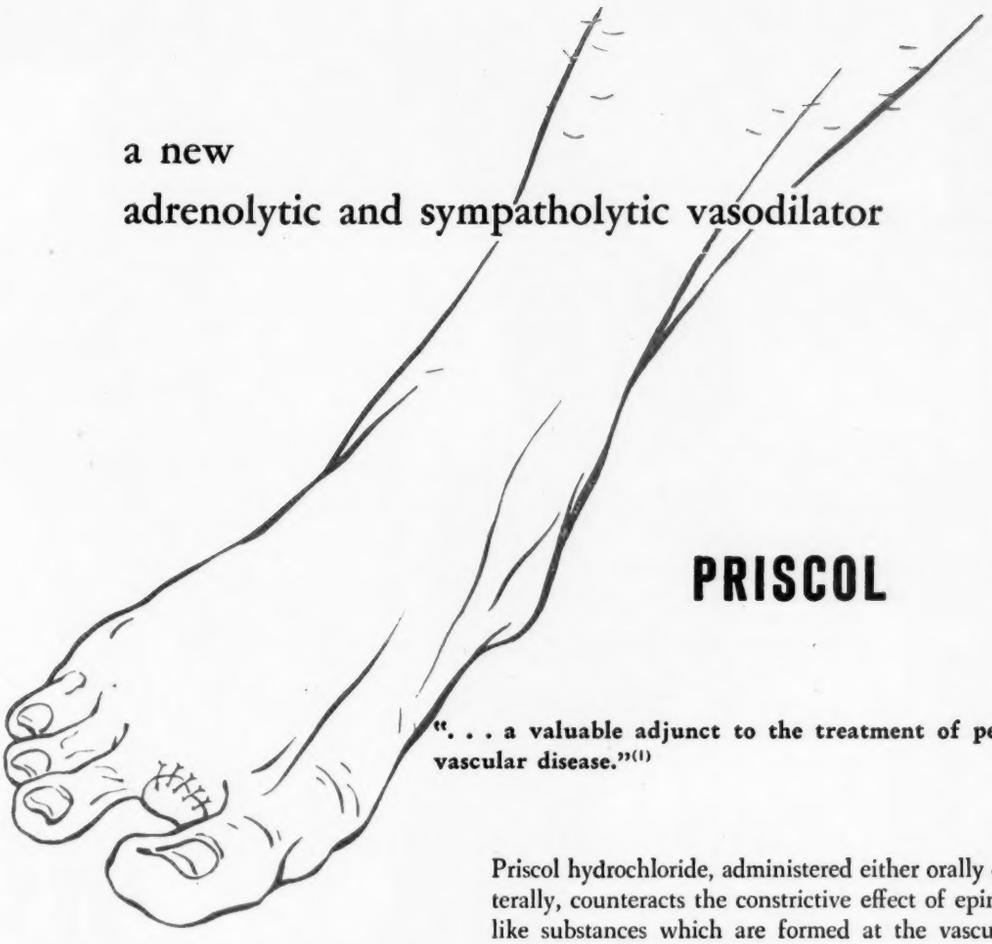

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1. Grimson, K. S., Marzoni, F. A., Reardon, M. J., and Hendrix, J. P.: *Surg.*, 23:728, 1948.

• Complete information may be obtained from

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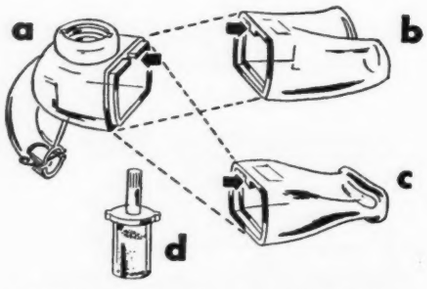

(a) Discharge chamber is attached either to (b) Mouthpiece or (c) Nosepiece for use with (d) Abbott Sifter Cartridge.

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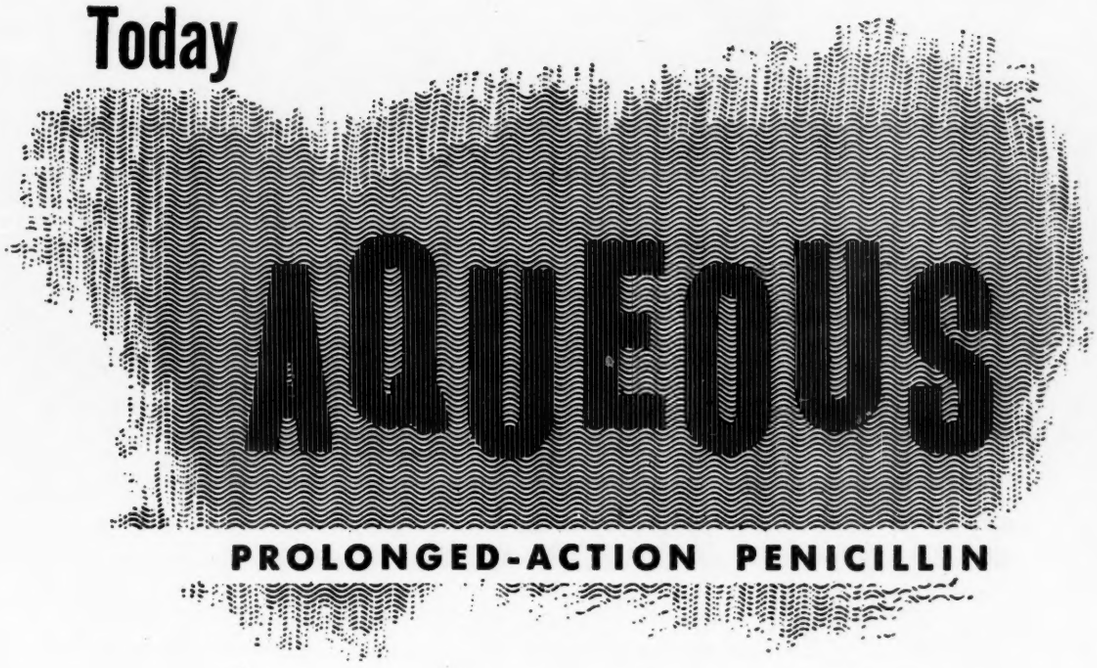

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CALCIUM	1.12 Gm.	VITAMIN C	30.0 mg.
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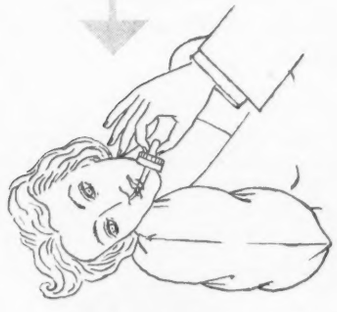

The head-low-lateral position is recommended for administration of **GLUCO-THRICIL**: adults, 2 to 4 drops in each nostril, three or four times daily; children, 1 to 2 drops in each nostril, three times daily. May also be given as spray or nasal pack

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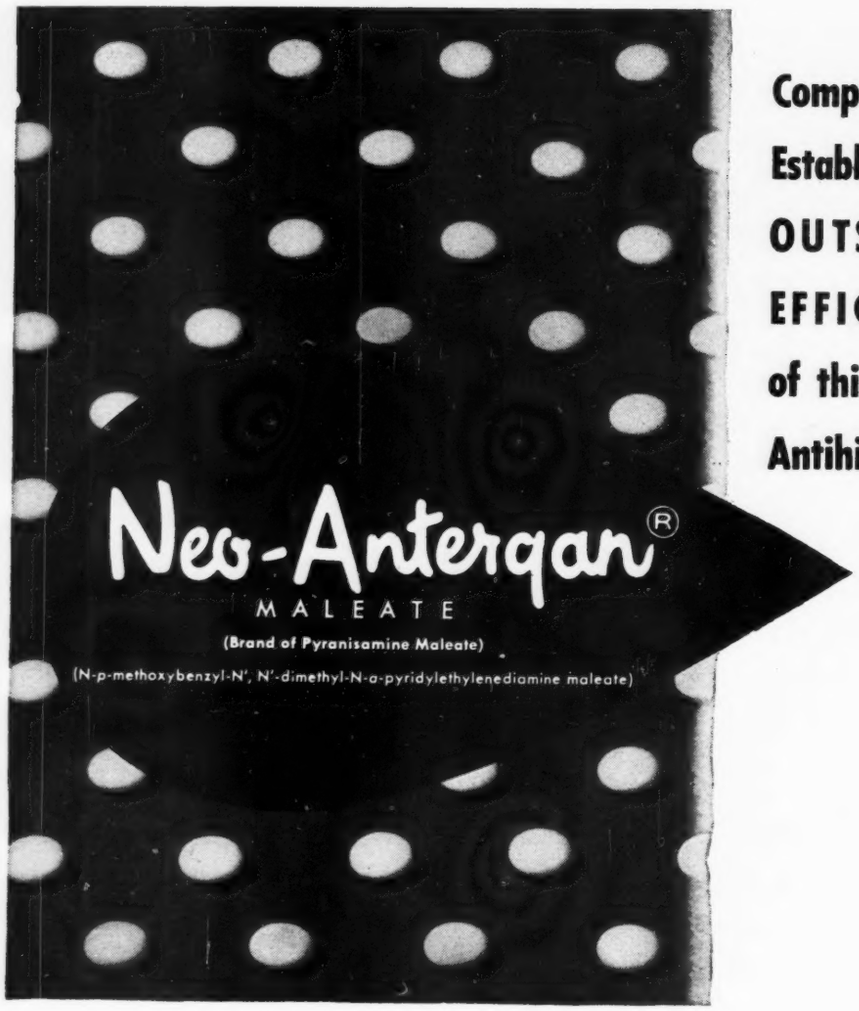

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**Friedlaender, A. S., and Friedlaender, S., Correlation of experimental data with clinical behavior of synthetic antihistaminic drugs. Paper read before Fourth Annual Session, American College of Allergists, New York City, March 12, 1948.*

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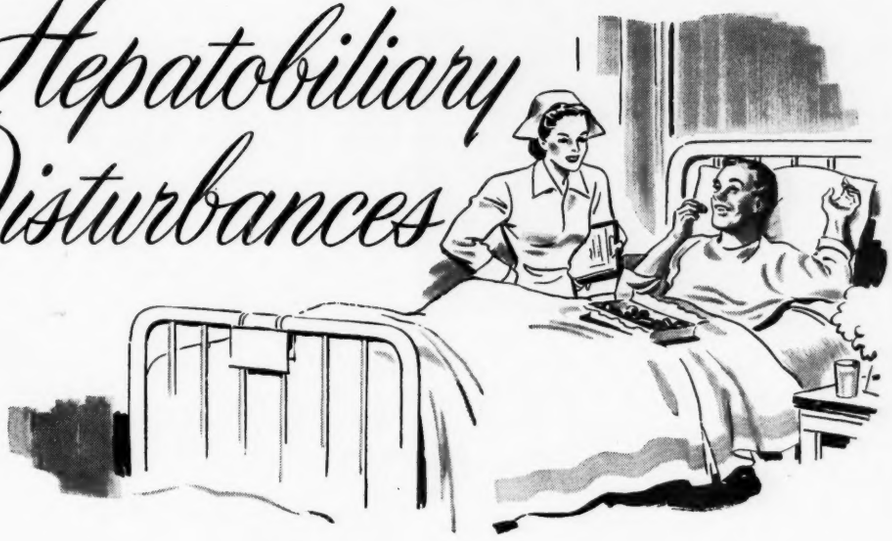
IN Hepatobiliary Disturbances



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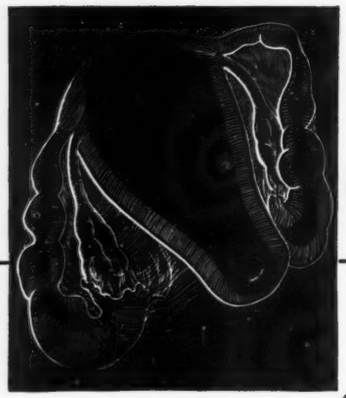
Hope for  the "pelvic cripple"...

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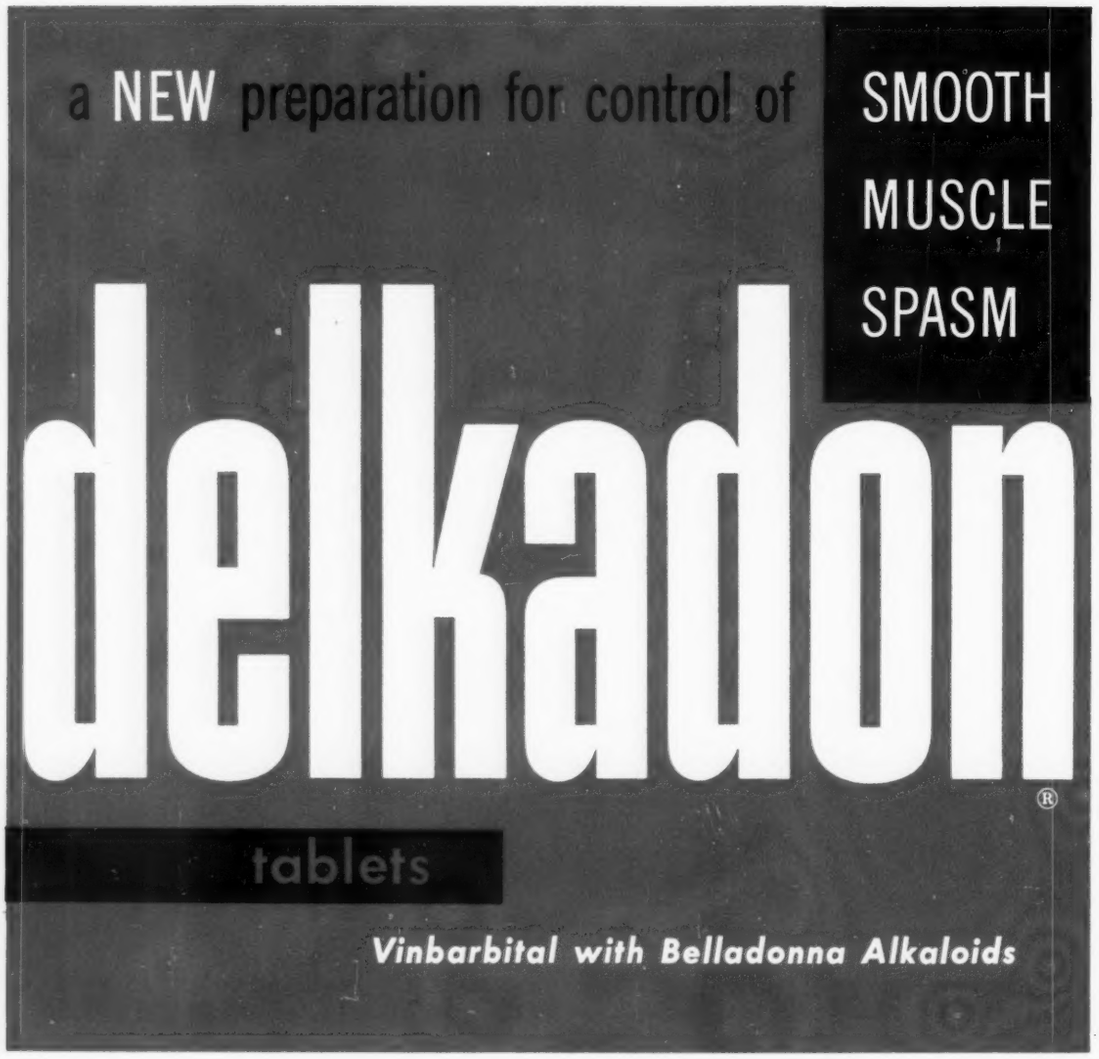

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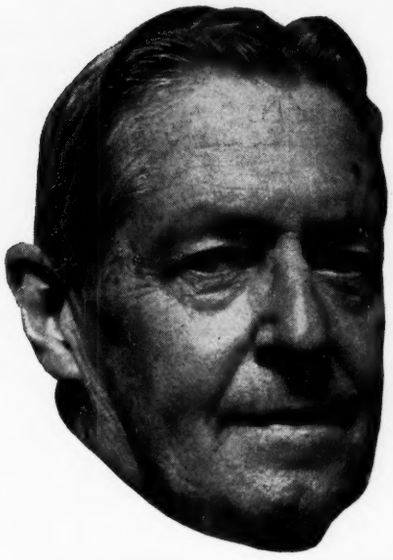

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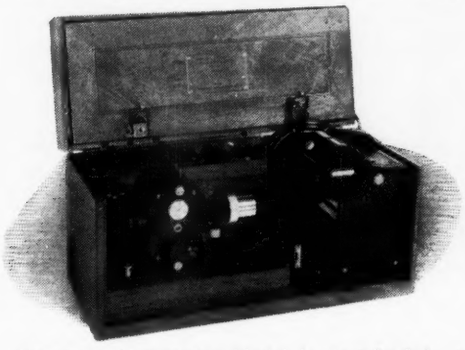

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Available, on prescription only, in specially-lined 1½ oz. tubes.

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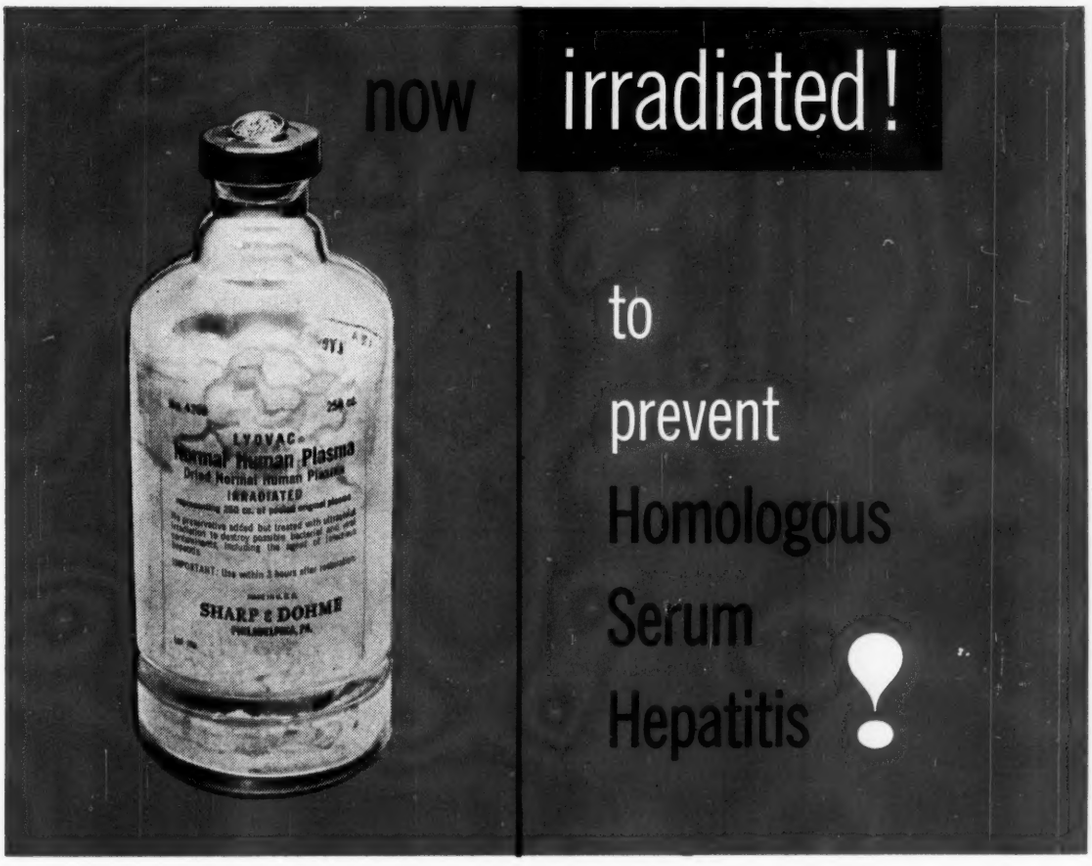

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1. Richards, M. B.: Brit. M. J. 1: 433 (1945).
2. Elvehjem, C. A., and Krehl, W. H.: J.A.M.A. 135: 279 (1947).

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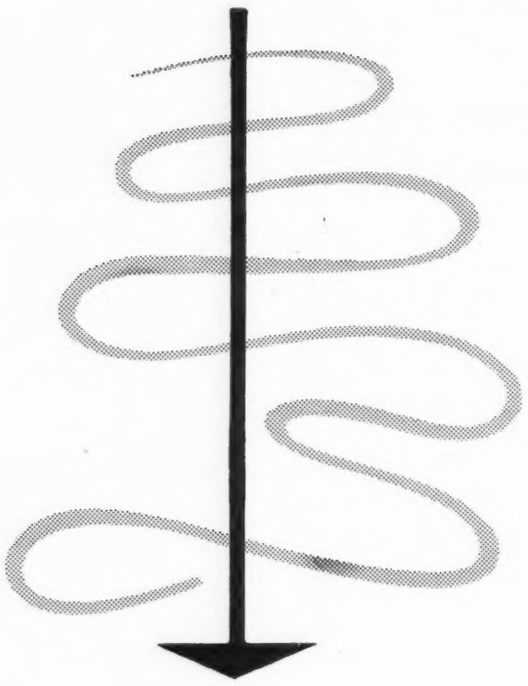

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The American Journal of Medicine

VOL. V DECEMBER, 1948 No. 6

Editorial

The American Journal of Medicine Seminars on Hypertension

In the first six issues of the current year The American Journal of Medicine was the forum for a series of seminars covering the field of experimental and human hypertension. These articles presented the seasoned opinions of a group of investigators with wide experience in one or another aspect of this problem. As was to be expected in a field of study which has not advanced to a point at which conclusive answers to crucial questions can be given, important differences in viewpoints were disclosed, not only with respect to the mechanisms responsible for the development of experimental renal and essential hypertension but also as to the relationship between the two conditions. That these controversial aspects could now be so clearly formulated as to provide specific challenges to be met by appropriate experimentation is in itself a sign of healthy progress. Any undue pessimism about the present state of the hypertension problem or its future development would seem unwarranted in the light of the extraordinary advances of the decade and a half since the classical experiments of Goldblatt ushered in the modern era in the study of hypertension.

What stands out as particularly characteristic of this period is the significant advance in experimental technics. The development by Goldblatt of a method by which hypertension could be produced regularly in animals provided the tool which made it possible to gain many new and important insights into the mechanisms by which hypertension might arise. More comprehensive and exact procedures for studying hemodynamics in animals and man furnished additional criteria for evaluating the relationship between essential hypertension and a variety of experimental hypertensive states in animals. The introduction, particularly by Smith and his associates, of more specific measures for estimating renal excretory function and blood flow has proved of special value in view of the central position which the kidney has tended to assume in this problem. In addition to these newer tools there has grown up a new way of thinking which utilizes a multi-disciplined approach in seeking to relate hypertension to underlying metabolic and endocrine processes.

Perhaps the outstanding result of the systematic exploration of experimental renal hypertension produced by the Goldblatt clamp or the perinephritic technic of Page was the accumulation of evidence that a humoral mechanism, primarily of renal origin, may play an important rôle in this syndrome. The elucidation of this mechanism, which began with the original experiments on renin by Tigerstedt and Bergmann in 1898, is a brilliant chapter in the history of hypertension. Only the barest outlines need be sketched here. The basic principle of this humoral mechanism is the kidney enzyme, renin. Undetectable in the blood under normal circumstances, applica-

tion of the Goldblatt clamp leads to its prompt appearance in measurable amounts in the renal vein, and later in the systemic, blood. Itself devoid of vasoconstrictor activity, it acts upon a pseudoglobulin substrate in plasma, termed hypertensinogen, to form the pressor principle, hypertensin (angiotonin), which is subsequently destroyed by an enzyme, hypertensinase, present in many tissues, including red blood cells. The analysis of the steps in this humoral mechanism is due in large measure to the efforts of many investigators in this country and South America, the work of Braun-Menendez and co-workers and of Page and his associates in identifying the pressor activity with hypertensin rather than renin representing a major contribution.

It is probable that this description of the renin-humoral system will prove to be essentially correct at least in its broader outlines; when the important components of the system have been isolated in pure form, it may require modification in certain details. The description is, however, still incomplete in at least one very important respect; there is no certain knowledge as to the nature of the stimulus which leads to the release of renin from the kidney. Of the two divergent viewpoints the more generally held is that renin discharge can best be related to renal ischemia. There is strong supportive evidence for the existence of renal ischemia immediately after application of the Goldblatt clamp, but it is still not established that a permanent reduction of renal blood flow is necessary for the persistence of hypertension in animals. Page and Corcoran, on the basis of renal blood flow and clearance studies, reject the ischemia concept and postulate that the release of renin is the result of an alteration in renal hemodynamics, most likely a reduction in intrarenal pulse pressure. However, the evidence offered by Page and his co-workers for renin release by kidneys perfused at low pulse pressures under aerobic conditions has been subjected to criticism on methodologic grounds.

The nature of the stimulus for renin discharge is not just of academic interest. The analysis of the mechanisms regulating renin metabolism within the kidney may well prove to be of primary importance for elucidation of the relation between experimental renal and essential hypertension. Except for the regular occurrence of renin in the kidney and its discharge following acute renal ischemia, there is virtually no knowledge of the factors which may condition its participation in the vascular economy of the organism. Does the renin mechanism take part in circulatory homeostasis under normal conditions or is it an emergency mechanism operative only in states of stress? Does it assist in regulating intrarenal hemodynamics under normotensive conditions by attaining local concentrations sufficient to induce renal arteriolar constriction but too low for peripheral pressor effects? What is the nature of the mechanisms by which renin is apparently retained within the kidney cell under certain conditions (e.g., aerobiosis) and released under others (e.g., anaerobiosis)? Does the kidney also possess a mechanism for inactivating renin? This possibility is suggested by the observation that when only one kidney is clamped and the other left intact, the resultant hypertension is transitory, presumably because of the protective action of the hypertrophied unclamped kidney. If such an inactivating mechanism exists, is it subject to deterioration under conditions other than anoxia and would its deterioration lead to an unrestrained release of renin even under aerobic conditions? These and other related questions urgently need answering. In the meantime we can scrutinize the present evidence for a causative rôle of this renal-humoral mechanism in experimental renal hypertension.

Two types of evidence are favorable to such a rôle. During the rise of blood pressure following partial constriction of the renal arteries renin appears in measurable and increasing amounts in the systemic circulation. Second, the intravenous injection of hypertensin in animals and man reproduces with reasonable fidelity the hemodynamic

picture characteristic of experimental renal and essential hypertension. Thus, hypertensin *could* produce the type of hypertension with which we are concerned, and abnormal amounts of its progenitor, renin, *are* present in the blood during the acute stage of experimental renal hypertension.

However, during the chronic stage of this syndrome, despite a persistent elevation of blood pressure, the renin content of the blood gradually falls until renin is no longer detectable by any of the present methods of assay. Several interpretations of this phenomenon have been advanced. The renin mechanism may play no significant rôle in the development of renal hypertension, the increased humoral content being coincidental rather than causal. Or the action of renin may be limited to initiation of the hypertensive syndrome which is subsequently maintained by other pressor agents or by a neurogenic mechanism mediated through the sympathetic nervous system as suggested by Ogden. An alternative hypothesis has been advanced by Grollman and his associates that the chronic stage of hypertension is due to the *lack* of some kidney principle which is essential for the maintenance of normal blood pressure. Finally, the possibility has been recognized that the absence of renin is only apparent and due to the lack of sensitivity of the current methods for its assay; thus, although the renin content of the blood during the chronic stage falls well below the measurable amounts characteristic of the acute stage of hypertension, the concentration may still be sufficiently great to maintain hypertension, particularly in an organism which in some manner may have become sensitized to its action.

At this juncture the renin theory received support of another character from the observations of Wakerlin and his associates that the repeated injection of heterologous renin extracts of kidney led to the development of antirenin activity in blood, caused a fall to normal of the blood pressure of dogs with renal hypertension and prevented the development of hypertension following constriction of the renal arteries. More recently Wakerlin has expressed some uncertainty because of discrepancies between antirenin titers in blood and the degree of protection observed, whether to attribute the modification of the hypertensive syndrome to antirenin or to immune bodies related to other as yet unknown principles in the renal extracts he employed as antigens. Goldblatt, however, does not consider conclusive the evidence upon which Wakerlin questions the significance of antirenin.

These uncertainties in regard to the rôle of renin, particularly in the chronic stage, have stimulated the search for other pressor agents which might be implicated in the development of renal hypertension. Suspicion first fell on the pressor amines, such as tyramine and hydroxytyramine, and was strengthened by the observation by Holtz that kidney pulp converted tyrosine into tyramine, particularly under anaerobic conditions, and by Bing that the totally ischemic kidney transformed dopa (*l*-di-hydroxyphenylalanine) into a pressor substance with some of the properties of hydroxytyramine. On the basis of these findings Schroeder injected tyrosinase intravenously into hypertensive dogs, rats and humans and observed a reduction in blood pressure which did not occur in normal controls. Despite this suggestive evidence, Page, in a review of the subject, concludes that there are many serious objections to the amine intoxication theory which militate against its playing an important rôle, at least in the early course of the disease; he lays particular stress on the significant differences between the hemodynamic phenomena of the pressor amines and those characteristic of experimental renal and essential hypertension.

Shipley, Helmer and Kohlstaedt recently described a pressor principle present in renal extracts and in the blood of cats dying of various causes or in hemorrhagic hypotension. Intravenous injection of such blood or renal extracts results in a sustained elevation of blood pressure in test animals

bilaterally nephrectomized thirty-six to forty-eight hours previously but not in normal controls. This principle appears to be protein in nature and distinct from renin and hypertensin as well as from the pressor amines. It has not as yet been found in the blood in hypertension. In view of its sustained pressor effect further study of this principle will be watched with great interest.

Another set of recently described vasotropic principles also distinct from renin and hypertensin has been found to be involved in the syndrome of experimental renal hypertension (Shorr, Zweifach, Furchgott, Mazur and Baez). These consist of a renal vasoexcitor, termed VEM, and a hepatic vasodepressor, VDM, with opposite actions on the muscular vessels of the terminal vascular bed just distal to the arterioles upon which hypertensin acts. VEM enhances the vasomotion and constrictor activity of the terminal arterioles and precapillary sphincters and increases their reactivity to topically applied epinephrine; VDM induces opposite effects on the same vessels. Their opposing actions on the terminal vascular bed are such as to suggest that they constitute a homeostatic system for the regulation of the peripheral circulation. VDM and VEM arise in liver and kidney, respectively, under anaerobic conditions; they are inactivated under aerobic conditions by the organs in which they are formed; these reactions are presumed to be of enzymatic nature.

These principles develop in experimental renal hypertension in the following manner: Within a few minutes of the application of the Goldblatt clamp, VEM, normally undetectable in blood by current assay methods, appears in renal vein blood and shortly thereafter in the systemic circulation. Its appearance has been traced to a deterioration following constriction of the renal arteries of the renal mechanism by which VEM formation is inhibited under aerobic conditions; as a result VEM is produced continuously under both aerobic and anaerobic conditions. VEM continues to be present in the blood throughout the period of rising blood pressure; however, when the chronic stage has set in, VEM usually is no longer detectable, a situation which at first appeared to be analogous to the disappearance of renin during the chronic stage. However, this "neutral" state of the blood was found to be due not to the disappearance of VEM (which by appropriate methods could be shown to persist in high concentrations) but to the appearance of equally high concentrations of VDM released by the liver. The nature and locus of action of VEM suggest that its potential effect upon peripheral resistance and blood pressure would be of an indirect and chronic character. Just what rôle these principles play in the genesis and perpetuation of renal hypertension remains a matter for further study.

This description of the humoral agents potentially involved in renal hypertension may be concluded with a consideration of the possible rôle of the adrenal cortical steroids, particularly those with the properties of desoxycorticosterone. On the clinical level the association of adrenal cortical overactivity in Cushing's syndrome with hypertension and nephrosclerosis is well established. Evidence of an experimental character has been provided by two types of procedures, ablation of the adrenals in animals with renal hypertension, and administration of desoxycorticosterone acetate (DOCA) or the induction of adrenal cortical hyperactivity.

Adrenalectomy usually results in the prompt disappearance of hypertension in dogs with renal hypertension and prevents its development following constriction of the renal arteries. A possible relation of these phenomena to the renin mechanism was indicated by the observation that although the renin content of kidneys of adrenalectomized dogs remains normal, there is a progressive fall in hypertensinogen which can be restored by the administration of DOCA. This is the basis for the suggestion that the inability of the adrenalectomized animal to maintain the hypertensive state

might in part be due to reduction in hypertensinogen, the formation of which in the liver may be dependent upon adrenal cortical function. It has also been found that kidneys from adrenalectomized animals lose the capacity to form VEM and that this function can be restored by DOCA or adrenal cortical extracts. Adrenalectomy also results in a progressive reduction in the response of the terminal vascular bed to the intravenous administration of VEM. Thus, removal of the adrenals results in certain modifications of two of the humoral systems which are suspect in renal hypertension.

Loeb was the first to report the hypertensive effects of DOCA given together with salt to patients with Addison's disease. Later studies in his clinic by Perera and co-workers showed similar effects in non-Addisonian and hypertensive subjects, an observation which has been confirmed by Schroeder. Selye has reported the development of hypertension and nephrosclerosis following DOCA in rats receiving high salt supplements; these effects could be prevented by the simultaneous administration of ammonium chloride. He also observed hypertension to follow the exposure of rats to a variety of stress situations which lead to chronic adrenal cortical hyperactivity. From these and other observations Selye would assign a primary rôle to the adrenal cortex in the genesis of hypertension. He postulates that a variety of appropriate stress situations, which lead through the anterior pituitary to adrenal cortical hyperactivity, would release large amounts of corticosteroids with properties similar to DOCA; these corticosteroids would then directly increase the production of pressor agents by the kidney, with resultant hypertension and nephrosclerosis.

There can be no doubt about the importance of the adrenal cortex for regulation of blood pressure; hypertension cannot be maintained in its absence. What remains for future study to establish is its exact rôle, whether as the prime mover or as an essential component of a complex system which can be activated or interrupted at a number of points.

The significance of these developments on the experimental level is in large measure dependent upon their relevance to the problem of essential hypertension in man, and it is on this point that we encounter the greatest divergence of opinion. Goldblatt has summarized the many resemblances between experimental renal and essential hypertension which have led him to conclude that a fundamental similarity exists between the two conditions. Favorable to their identity is the existence of a chronic benign and a malignant phase of experimental renal hypertension with retinal and renal excretory changes comparable to those seen in the analogous stages of essential hypertension in man. The hemodynamics are also similar in both conditions. Furthermore, occasional cases are encountered in man in which unilateral renal disease, due to vascular anomalies or chronic inflammatory disease, is associated with hypertension corrected by removal of the involved kidney.

The status of the relation of the renin-hypertensin system to essential hypertension is essentially the same as for experimental renal hypertension. Its implication is favored by the fact that administration of hypertensin to animals and man elevates both systolic and diastolic pressures and produces changes in renal blood flow comparable to those found in essential hypertension. Less conclusive are the results of the assay for renin. As pointed out in Dexter's review, although renin had been found in the blood for short periods of time in a few instances of acute hypertension resulting from glomerulonephritis and eclampsia, efforts to detect renin in chronic essential hypertension had been as uniformly unsuccessful as in the chronic stage of experimental renal hypertension. However, since Dexter's review was written, Fasciolo and Taquini have developed a more sensitive method for renin assay by means of which they were able to demonstrate its presence in chronic

essential hypertension but in no greater amounts than in normotensive subjects.

Recently new evidence of a similarity between these two conditions has been provided by the observations of Shorr and Zweifach that the high concentrations of VEM and VDM previously noted in the blood during the chronic stage of renal hypertension in dogs are also regularly present in chronic essential hypertension in man.

The opposite viewpoint has been vigorously presented in these seminars by Goldring and in a review in this Journal by Smith. They point out that those instances in which unilateral renal disease is responsible for hypertension represent only a small fraction of the cases of essential hypertension. Furthermore, there is no greater incidence of hypertension in urologic conditions associated with unilateral renal disease than in the general population. The analysis by Chasis and Redish of the renal blood flow and excretory function of both kidneys in essential hypertension revealed no significant differences to justify the inference that a unilateral reduction of renal blood flow could be responsible for the initiation of hypertension.

They do, however, recognize that the generalized increase in peripheral resistance in essential hypertension, the increased constriction of the renal blood vessels, including both afferent and efferent glomerular arterioles and its reversibility by pyrogenic agents, as well as the persistence of impaired renal blood flow following sympathectomy, all make it necessary to assume the participation of a humoral pressor agent. But they find it difficult to relate this humoral pressor agent to the kidney in terms of the renal hypertension experiment of Goldblatt. They point out that although there is usually some reduction in blood flow and renal excretory function, essential hypertension can exist typically with no significant impairment of either index. Thus, if the pressor agent is of renal origin and if renal ischemia is essential for its production, there is no present knowledge as to the way in which ischemia is initiated. That it does not result from primary vascular disease is evident from the many instances of essential hypertension unaccompanied by vascular disease. The link which they regard as essential for establishing the identity of experimental renal and essential hypertension is therefore missing. It is, for Smith, "illogical to suppose that at one moment humoral agents are operating to reduce renal blood flow and then at the next moment suppose that the reduction in blood flow is the reason for the appearance of these agents in the blood." If hypertensive disease is the result of myriads of clamps on renal arterioles in consequence of arteriolar sclerosis, then the arteriolar disease which remains unexplained is the primary event and not limited to the kidney. In short, the kidney appears to be the victim rather than the culprit although once involved it may play an accessory rôle.

Goldblatt's position with respect to these objections is as follows: To regard the experimental type of hypertension as necessarily dissimilar to essential hypertension because the main renal artery of humans with hypertension is not frequently stenotic is to misinterpret the main purpose and significance of the experimental procedure. The constriction of the main renal artery was an expedient resorted to as most likely to reproduce the circulatory disturbance of the kidney resembling the most probable effect of *intrarenal* stenosing arterial and arteriolar sclerosis. Those instances in man in which unilateral kidney disease leads to hypertension are therefore not to be regarded as etiologically typical but rather as important evidence that some type of alteration in renal blood flow can also cause a condition in man similar in its clinical manifestations to typical essential hypertension. There is no good *a priori* reason why experimental constriction of the main renal artery should not be considered capable of reproducing the functional state of the human kidney in essential hypertension. The ultimate decision must rest upon facts, of which an impressive number

have been accumulated which favor a similarity between experimental renal and essential hypertension and hence the primary renal origin of the latter.

However, to the problem posed by Smith as to the primary or secondary character of the changes in the renal circulation in essential hypertension there is admittedly no present answer. Indeed this question represents the core of the difficulty in reconciling these divergent viewpoints. Goldblatt's present position may be interpreted as favoring some antecedent intrarenal arterial and arteriolar sclerosis as the initiating factor for the renal humoral mechanism. Even were these renal vascular changes part of a more generalized vascular process, he suggests that their significance for peripheral vascular resistance would be greater because of their relation to the renal pressor mechanism for which no counterpart has as yet been found in other tissues. Thus for Goldblatt the cause of vascular disease now becomes the most important problem for future investigation of the pathogenesis of hypertension.

It is possible that both positions are somewhat too rigidly formulated as regards the potential primary rôle of the kidney in essential hypertension. There may be a middle ground between antecedent renal vascular disease and renal vasospasm secondary to extrarenal pressor agents which might profitably be explored. Such an alternative is advanced in the statement by Smith and co-workers that "the possibility cannot as yet be excluded that the appearance of pressor and cytotoxic substances in the blood follows a metabolic disorder in the kidney or other organs and is wholly independent of renal ischemia." This statement does not, of course, exhaust the many possibilities inherent in this provocative suggestion as, for example, the deterioration of an enzymatic system regulating a renal humoral mechanism through repeated exposures to brief periods of ischemia of, say, neurogenic origin, and the subsequent persistence of this metabolic disorder independent of sustained renal ischemia.

The full exploration of these possibilities will be feasible only when all the details are known not only of the intermediary metabolism of the renal-humoral mechanisms but also of the factors, intra- and extrarenal, by which their metabolism may be influenced. How far we are from this goal in the case of the renin system has already been indicated. However, some idea of the type of situation which may prevail might be gained from the still incomplete picture of the mechanisms governing the metabolism of the hepatorenal vasotropic factors, VEM and VDM. Each of these principles is formed under anaerobic, and inactivated or its formation inhibited under aerobic conditions, a situation analogous to the Pasteur reaction which restricts lactic acid formation by normal tissues to anaerobiosis. These reactions appear to be under enzymatic control; preliminary studies of the liver VDM inactivation system indicate the participation of a protein apoenzyme and a heat-stable, dialyzable co-enzyme whose effects can be reproduced by muscle adenylic acid. These reactions as a whole may be regarded as intracellular homeostatic systems by which the supply of VDM and VEM could be adjusted to the circulatory requirements of the organism.

However, this intracellular regulation of both anaerobic and aerobic phases of these systems in liver and kidney can be regularly disturbed by specific variations in environmental conditions. Thus, the VDM inactivation system of the liver undergoes deterioration during the hypoxia of that organ in irreversible shock as well as after a two-hour exposure to anoxia *in vitro*. It is also damaged in rats with nutritional cirrhosis due to low-protein, high-fat diets. A brief exposure of the kidney to anoxia *in vitro* results in a loss of the capacity to prevent the aerobic formation of VEM; more prolonged anoxia, *in vivo* and *in vitro*, causes a total loss of the ability to form VEM as does fasting or a low-protein diet. Adrenalectomy also abolishes VEM formation; this can be restored by DOCA or adrenal cortical extracts but not by salt.

Of particular interest in the problem of hypertension is the loss, following partial constriction of the renal artery, of the capacity of the kidney to inhibit the aerobic formation of VEM. This defect persists as long as the clamp is in place even though the normal oxygen consumption of the kidney, as determined *in vitro*, might suggest the return of an adequate supply of oxygen to the kidney *in vivo*. It is as a result of this defect that VEM appears in blood throughout the hypertensive syndrome, predominating in the acute phase, but accompanied by equivalent amounts of VDM during the chronic stage. Since studies by Bradley have shown that the hepatic blood flow in hypertension is unimpaired, liver hypoxia would not seem to be responsible for the release of VDM during the chronic stage. It is suggested that the stimulus may be the presence of abnormal amounts of the oppositely-acting VEM, an inference consistent with the dynamics of a homeostatic system. This last observation is of special interest as indicating, at least for this set of vascular principles, that other factors than ischemia may lead to derangements similar to those caused by ischemia.

The derangements of the renal VEM mechanisms by short periods of anoxia call to mind the attempts to induce hypertension by repeatedly subjecting the kidney to brief periods of ischemia on the theory that irreversible changes in the renal humoral mechanisms might eventually result. Unfortunately, interpretation of the positive results reported is clouded by the damage usually sustained by the renal blood vessels from the manipulation involved. In man, also, increasing attention is being focused on the consequences for hypertension of repeated exposures to the transitory reduction in renal blood reported to result from a variety of painful or emotionally distressing stimuli. In this connection the possible relation of the intrarenal vascular shunts, studied by Trueta and coworkers, to renal cortical ischemia is of considerable interest but still remains to be established.

These observations on the VEM-VDM systems are set forth in some detail for the suggestions inherent in them of the ways by which the renin system or any other renal-humoral vasoactive system might be similarly studied. The ultimate goal of such an investigation may be reached only when all of the reactions involved are understood, the modifying circumstances, intrinsic and extrinsic, recognized and the active principles and enzyme systems concerned isolated in pure form. Only then may it be possible to assess conclusively the rôle of the renal-humoral systems in hypertension and to explore the therapeutic avenues which might be opened, secure from the objections to which previous efforts with impure materials have been so vulnerable.

It would extend this already lengthy survey unduly to enter into the many controversial aspects of the present medical and surgical treatment of essential hypertension. The reader will find them vigorously set forth in the seminars by Kempner, Schroeder, Smithwick, Goldring and the review by Smith. Here he will find every shade of opinion as to their effectiveness, from the highly favorable to the verdict of "experimentation based on desperation." Such differing judgments by students observing much the same material must certainly in considerable measure depend upon the particular yardstick employed, whether cure or amelioration. Whatever the standards, they should be applied with caution lest, on the one hand, therapeutic endeavors be discouraged by setting the sights too high or, on the other, scientific judgment give way to an undiscriminating pragmatism. A good deal of criticism has with reason been levelled at the lack of adequate control observations in many therapeutic studies. An adequate base line, such as is outlined by Perera's studies, is essential for the evaluation of therapy in a condition such as hypertension which is so prone to non-specific spontaneous variations, particularly in regard to the level of the blood pressure, the index most commonly used. It would seem unwise, however, to neglect

the potential significance of any evidence, provided it is soundly documented, even though it is based upon partial relief and on the response of only a proportion of the patients treated. The syndrome is highly complex; it undoubtedly varies in the degree to which one or another element predominates and in the extent to which various derangements are reversible at any stage in its evolution.

It would be a happy circumstance indeed to be able to conclude this survey of experimental renal and essential hypertension by a synthesis of what is known into a structure whose pattern, although incomplete, is nevertheless architecturally harmonious. As it stands, however, the foundations are still fragmentary, the main arch still lacks a keystone and there is no unanimity about the grand design. In spite of this a structure is slowly but steadily taking form and it is a presage of its eventual soundness that each brick, stone and girder is being rigorously tested before it is put in place. And in this process we must not undervalue the constructive force of the creative imagination just because it has fashioned a variety of designs from the same raw material.

The richness of the raw material which has been accumulated over the past fifteen years and the avenues which have been opened for further exploration should, with reason, temper our reaction to the one conclusion about which there is general agreement—that at present the origin of essential hypertension remains unknown. That this conclusion has been accepted as a challenge rather than a sign of defeat is evident from the intensification of the efforts which are being directed at this problem whose urgency hardly needs emphasizing. Smith, from a survey of data supplied by the Bureau of the Census, calculated that about one million persons above the age of forty-five die in this country every year; of this number approximately 450,000 die of one or another sequela of cardiovascular renal disease, nearly five times as many as die of cancer. A large fraction of cardiovascular renal disease is hypertensive in origin, presenting us with what is perhaps medicine's major problem. It is regrettable that compared with some other areas of medicine, research in cardiovascular disease has hitherto received support in a measure that is so poorly commensurate with its importance. There are, however, encouraging signs that this situation is on the way to being corrected in the increased support which is becoming available from private and public sources. The new National Heart Institute, which has been set up under the direction of Dr. C. J. Van Slyke, is the most recent expression of the increasing awareness of public responsibility for this major aspect of the health of the nation.

In this survey it has not been feasible to document the contents with bibliographic references or to cite all the meritorious studies in the very voluminous literature. Its main purpose has been to assist the reader in steering a course through the maze of data, frequently of a conflicting character, which has accumulated and, more especially, to send him back to the seminars themselves. The interested reader may also consult with profit the excellent translation by Dexter of the monograph by Braun-Menendez and co-workers on Renal Hypertension, the First Conference on Factors Regulating Blood Pressure, published by the Josiah Macy, Jr. Foundation, and the recent Symposium on Hypertension of the New York Academy of Sciences.

EPHRAIM SHORR, M.D.

Clinical Studies

The Hemodynamic Response of Man to Nor-Epinephrine and Epinephrine and Its Relation to the Problem of Hypertension*

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THE present study was undertaken in order to evaluate the possible rôle of the sympathetic nervous system in the mechanism of essential hypertension, employing the response to *l*-nor-epinephrine and *l*-epinephrine as a means of investigation.

NOR-EPINEPHRINE

Nor-epinephrine (nor-adrenaline, arterenol, amino-ethanolcatechol) is a primary amine identical with epinephrine except for the absence of a methyl group on the nitrogen atom. (Fig. 1.) It was first synthesized by Stolz[37] in 1904. Recently it has been suggested as a possible precursor of epinephrine *in vivo*[5] since it has been shown that methylation occurs readily in the body.[11] The levo-isomer, possessing approximately twice the activity of the optically inactive preparation, became available in 1948 following resolution of the racemic mixture by Tainter and his group.[38]

The consistency with which the actions of nor-epinephrine reproduce those of stimulation of sympathetic excitor nerves has led competent investigators to the conclusion that it may be sympathin E, as first suggested by Bacq.[2] In support of this hypothesis Stehle and Ellsworth[36] and Greer and his co-workers[20] demonstrated the striking similarity between the effects of nor-epinephrine and those produced by stimulation of the hepatic sympathetic nerves. These observations have been confirmed by von Euler[12,13] and Gaddum and Goodwin.[18]

The strongest evidence in favor of this assumption was von Euler's demonstration in 1946 of a substance in mammalian adrenergic nerves indistinguishable from nor-epinephrine by biologic and crude chemical tests.[12,13] The thoracic and lumbar sympathetic chain and the splenic periarterial nerves of cattle were particularly suitable sources and contained the equivalent of 10 to 25 μg. of *d,l*-nor-epinephrine per Gm. of tissue. This substance differed from epinephrine in its blood pressure action following ergotamine. Ergotamine reverses the pressor effect of epinephrine but not of nor-epinephrine. This substance differed likewise from epinephrine in its action on the non-pregnant cat uterus in that relaxation was inconspicuous.

It has been assumed that each of the transmitters, epinephrine and nor-epinephrine, carries excitor or inhibitor functions exclusively. But this does not appear to be so because excitor functions are carried not only by nor-epinephrine but also by epinephrine. Epinephrine has been proved to be the transmitter of sympathetic excitation in

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certain areas, namely, the heart and the vessels of the skin.[17,24]

Whereas epinephrine shows a complex of pharmacologic actions composed of both excitor and inhibitor functions, in nor-epinephrine the excitor functions prevail. Barger and Dale[4] in 1910 demonstrated that introduction of a methyl radical into the amino group produced inhibitory actions in various sympathomimetic amines. The pressor effect of *d,l*-nor-epinephrine was greater than that of *d,l*-epinephrine, and the relaxation of the non-pregnant cat uterus was inconspicuous.

A recent study by West[40] gives a summary of previous investigations and a comparison of pharmacologic responses to nor-epinephrine and epinephrine. Tainter[38] found that the acute toxicity of intravenously injected *l*-nor-epinephrine in mice was only one third that of *l*-epinephrine. For equivalent pressor doses *l*-nor-epinephrine had a safety ratio (toxicity to pressor activity) which was four times that of *l*-epinephrine. No studies of nor-epinephrine in man have been published up to this time.

EPINEPHRINE

The classic pharmacologic conception of the pressor action of epinephrine is that it depends chiefly on intense vasoconstriction, the direct cardiac action being only accessory. The hypotensive action of epinephrine in small doses, reported as early as 1900[28] and extensively studied by Cannon and Lyman,[8] has been generally regarded as of minor physiologic importance.

Starr and his co-workers[33] and Ranges and Bradley,[31] using ballistocardiographic output determinations, found that subcutaneous administration of therapeutic amounts of epinephrine in man resulted in increased cardiac output, decreased peripheral resistance and diastolic pressure with only a small elevation of systolic tension. Starr attributed the observed drop of total peripheral resistance, which seemed to contradict common pharmacologic experience, to the subcutaneous route of administration with resulting slow resorption of minute amounts of the drug.

McMichael and Sharpey-Schafer,[27] using the direct Fick method, observed an increased cardiac output after minute amounts of epinephrine insufficient to alter the blood pressure, pulse rate or intra-auricular pressure, findings compatible with a fall in peripheral resistance. The studies on muscle blood flow in man by Allen, Barcroft and Edholm[1] show a significant vasodilator response during intravenous infusion of epinephrine in average doses of 10 μg./min.

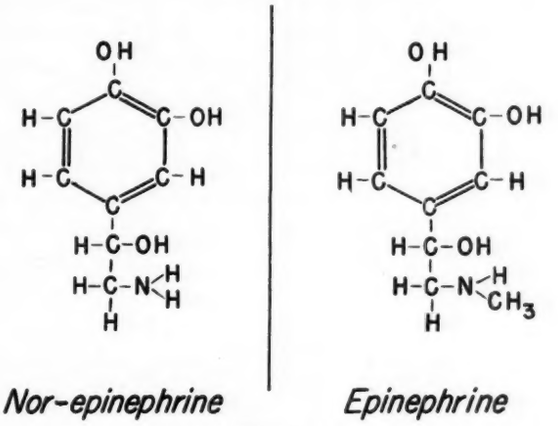


FIG. 1.

The results of these studies raise the question whether the doses used are comparable to a physiologic rate of release of epinephrine in man. In this case one would expect the vascular effect of epinephrine under physiologic conditions to be predominantly inhibitory.

A uniform increase of peripheral resistance has been commonly accepted to be present in essential hypertension.[29,30,35] If essential hypertension is due to an increase of sympathetic activity in the arterial tree, it should be possible to reproduce its hemodynamics by an intravenous infusion of the sympathetic transmitter. This method was used by Fatheree and Hines[15] who studied the changes in blood pressure and pulse rate following epinephrine infusion in normotensive and hypertensive subjects. Whereas elevation of diastolic pressure is a characteristic feature of essential hypertension, epinephrine caused only an in-

significant increase of diastolic blood pressure in normotensive subjects. The diastolic pressure was decreased in hypertensives. They attributed the concomitant rise of systolic blood pressure to increased cardiac activity and the relatively slight rise or decrease in diastolic pressure to peripheral vasodilation. As long as epinephrine was regarded as the only sympathetic transmitter this study would appear to exclude increased sympathetic activity as an important mechanism in essential hypertension. The recent evidence of the dual nature of the sympathetic chemical mediators[3,12,13] made it desirable to re-investigate the problem.

METHODS

In preliminary studies the systemic blood pressure and pulse rate of twenty hospital patients without cardiovascular disease, fourteen patients with uncomplicated essential hypertension, one patient with chronic nephritis and one patient with chronic hypertensive cardiovascular disease in failure were observed during a continuous intravenous infusion of nor-epinephrine, epinephrine or a mixture of the two, the latter given only to normals. The solutions were made up to contain 4 micrograms of nor-epinephrine or epinephrine per ml. of saline. During the preliminary studies *d,l*-nor-epinephrine was used until *l*-nor-epinephrine became available.

With the patient at rest, normal saline was infused. When the arterial blood pressure and pulse became stabilized, a three-way stopcock was turned to the drug infusion which was first allowed to flow at the rate of 0.05 μg./Kg./min. of the test substance. The highest amount of *l*-nor-epinephrine given in these experiments was 0.4 μg./Kg./min. The pulse and systemic blood pressure, obtained by cuff, were observed about every two minutes. The dosage was regulated in such a manner as to obtain significant responses in normals and, on the other hand, to keep the pressure response in hypertensives below spontaneous peak levels.

In eight patients with normal blood pressures and three patients with uncomplicated hypertension, intra-arterial pressures and cardiac output determinations, using the direct Fick method, were obtained before and during such drug infusions. The mixed venous blood was withdrawn anaerobically from an intracardiac catheter placed in the right or left pulmonary artery about 3 cm. from the bifurcation. The arterial blood was obtained from an indwelling arterial needle seated in either a brachial or femoral artery. The oxygen contents of these blood samples was determined immediately by the manometric method of van Slyke and Neill. Duplicate blood samples were required to check within 0.2 volumes per cent. The expired air was measured and collected in a Tissot spirometer and duplicate aliquot samples analyzed for oxygen and carbon dioxide in a Haldane apparatus. The systemic and pulmonary arterial pressures were recorded by Hamilton manometers immediately before and after each cardiac output determination and the mean pressures obtained by planimetric integration of the pressure tracings. The total peripheral resistance (TPR) expressed in dynes cm.$^{-5}$ sec. was calculated from the following formula:

$$\text{TPR} = \frac{\text{mean arterial pressure mm. Hg}}{\text{cardiac output L. per second}} \times 13.32^{*}$$

The value of the mean arterial pressure used in this calculation was the mean of the two observations made directly before and directly after the blood sampling for the cardiac output determination. These values rarely varied by more than 3 or 4 mm. of mercury.

The patients were studied in the postabsorptive state. All but one received 0.1 Gm. of sodium pentobarbital by mouth before reaching the laboratory. Immediately after introduction of the catheter into the pulmonary artery and placement of the intra-arterial needle an intravenous saline infusion was started. Usually within ten to fifteen minutes following these manipulations the patients were in a sufficiently stable resting state to make the first group of control measurements. A second group of baseline observations were made following a fifteen to thirty-five-minute rest period. Thereupon, epinephrine or nor-epinephrine was given as previously described at a rate determined by a previous sensitivity test. The pulse rate and blood pressures by cuff were checked to select a significant blood pressure increase with a constant level for further observations. The first Hamilton manometer pressure recordings and cardiac output determinations were obtained

* 13.32 = specific gravity of mercury.

TABLE I

CARDIOVASCULAR RESPONSE OF EIGHT NORMOTENSIVE AND THREE HYPERTENSIVE PATIENTS TO INFUSIONS OF *l*-EPINEPHRINE AND *l*-NOR-EPINEPHRINE

I. Patients without Cardiovascular Disease: During successive infusions of *l*-epinephrine, *l*-nor-epinephrine, and *l*-nor-epinephrine + *l*-epinephrine

Case	Time	State, Drug	Dose μg./kg./min.	Pulse	Mean Pulmonary Arterial Pressure (mm. Hg)	Systemic Arterial Pressure			Ventilation L/min./sq. m.*	Oxygen Intake cc./min./sq. m.†	Arteriovenous Oxygen Difference (volumes per cent)	Cardiac Output L./min.	Total Peripheral Resistance (dynes cm.$^{-5}$ sec.)
						Systolic	Diastolic	Mean					
						mm. Hg	mm. Hg	mm. Hg					
I. J. S., twenty-six yr., male; body surface, 1.81 sq. m.	9:40	rest	....	64	14	120	68	86	2.9	144	3.5	7.46	922
	9:54	rest	....	60	14	121	70	88	3.1	145	3.9	6.72	1030
	10:14	*l*-epinephrine fourteen minutes	0.15	78	22	147	72	96	4.1	176	2.4	13.30	577
	10:35	rest	....	60	14	133	76	94	2.7	142	4.1	6.24	1205
	10:56	*l*-nor-epinephrine fourteen minutes	0.15	48	19	162	91	115	3.0	143	5.0	5.18	1785
	11:13	*l*-nor-epinephrine *l*-epinephrine twelve minutes	0.15 0.15	58	25	174	83	111	3.6	168	3.3	9.22	960
II. T. R., thirty-seven yr., male; body surface, 1.84 sq. m.	9:28	rest	....	68	10	141	71	95	3.0	111	3.2	6.33	1197
	9:50	rest	....	68	12	143	74	97	3.3	126	3.8	6.09	1270
	10:11	*l*-nor-epinephrine twelve minutes	0.16	53	18	191	90	122	4.0	153	3.9	7.20	1354
	10:26	*l*-nor-epinephrine *l*-epinephrine ten minutes	0.15 0.15	78	20	172	75	105	4.6	184	2.9	11.68	714
	10:43	*l*-epinephrine eleven minutes	0.16	96	14	143	66	91	4.8	195	2.5	14.37	500
	11:17	rest thirty minutes	....	80	9	125	69	88	4.3	178	4.4	7.46	942
III. E. G., thirty yr., male; body surface, 1.74 sq. m.	9:45	rest	....	78	16	124	78	98	4.2	138	3.4	7.04	1102
	9:57	rest	....	72	16	120	75	94	4.7	166	3.5	8.23	909
	10:16	*l*-epinephrine thirteen minutes	0.25	72	25	180	87	118	6.2	206	2.3	15.56	601
	10:40	rest	....	68	16	122	81	101	3.9	140	3.3	7.39	1090
	10:56	*l*-nor-epinephrine twelve minutes	0.25	50	22	184	106	138	3.9	140	4.3	5.68	1915
IV. C. G., forty-five yr., male; body surface, 1.81 sq. m.	9:42	rest	....	62	12	120	62	84	3.4	140	4.1	6.18	1086
	10:06	*l*-epinephrine fourteen minutes	0.30	68	22	162	65	98	4.9	182	3.0	10.97	714
	10:25	*l*-epinephrine thirty-seven minutes	0.28	86	20	164	70	101	5.8	189	2.3	14.82	545
	10:49	rest twenty-three minutes	....	72	10	118	63	85	4.3	177	3.8	8.43	808
	11:08	*l*-nor-epinephrine fifteen minutes	0.28	54	14	162	83	109	5.7	204	4.5	8.18	1060
During infusion of *l*-nor-epinephrine alone													
V. B. H., twenty-five yr., male; body surface, 2.00 sq. m.	10:20	rest	....	87	17	120	71	90	4.8	183	3.8	9.61	748
	10:55	rest	....	75	18	132	80	99	5.2	194	3.8	10.20	776
	11:25	*l*-nor-epinephrine twenty-two minutes	0.11	60	21	160	84	113	6.2	220	4.1	10.73	838
	11:35	*l*-nor-epinephrine thirty-two minutes	0.125	58	20	156	85	110	7.1	228	4.5	10.10	871

TABLE I (*Continued*)

Case	Time	State, Drug	Dose μg./Kg./min.	Pulse	Mean Pulmonary Arterial Pressure (mm. Hg)	Systemic Arterial Pressure			Ventilation L./min./sq. m.*	Oxygen Intake cc./min./sq. m.†	Arteriovenous Oxygen Difference (volumes per cent)	Cardiac Output L./min.	Total Peripheral Resistance (dynes cm.$^{-5}$ sec.)
						Systolic	Diastolic	Mean					
						mm. Hg	mm. Hg	mm. Hg					
VI. S. T., Forty-eight yr., male; body surface, 1.88 sq. m.	9:45	rest	....	92	5	132	78	97	5.8	149	3.7	6.38	1206
	9:59	rest	....	88	5	140	82	102	4.8	136	3.8	5.66	1440
	10:27	*l*-nor-epinephrine fourteen minutes	0.16	72	17	168	92	120	4.3	159	4.0	6.30	1518
	10:42	*l*-nor-epinephrine twenty-nine minutes	0.12	72	17	176	94	125	7.2	198	3.9	8.03	1240
VII. F. P., twenty-eight yr., male; body surface, 1.85 sq. m.	9:40	rest	....	67	7	114	68	86	2.8	109	3.7	4.71	1453
	9:53	rest	....	68	7	117	68	89	3.0	118	3.5	5.40	1317
	10:30	*l*-nor-epinephrine twenty minutes	0.24	52	11	165	90	118	3.5	143	4.6	4.95	1900
	10:45	*l*-nor-epinephrine thirty-five minutes	0.19	59	9	161	89	118	4.2	164	4.4	5.98	1570
VIII. E. B., twenty-two yr., male; body surface, 1.85 sq. m.	9:35	rest	....	91	16	107	68	79	3.9	148	3.5	7.82	806
	9:48	rest	....	92	19	108	72	80	3.4	144	3.4	7.82	818
	10:15	*l*-nor-epinephrine fifteen minutes	0.40	58	38	156	93	114	4.5	170	5.0	6.30	1448
	10:30	*l*-nor-epinephrine thirty minutes	0.30	63	34	160	95	118	4.5	175	4.0	8.08	1168
II. Patients with Essential Hypertension: During infusion of *l*-epinephrine and, in one case, *l*-nor-epinephrine													
IX. A. B., forty-six yr., male; body surface, 1.95 sq. m.	2:13	rest	....	74	13	194	113	142	3.9	138	4.6	5.85	1920
	2:20	rest	....	72	14	189	111	139	3.8	141	4.4	6.24	1770
	2:44	*l*-epinephrine ten minutes	0.07	84	20	193	105	137	4.3	152	3.6	8.26	1315
	2:54	*l*-epinephrine twenty minutes	0.14	90	21	209	115	147	5.5	205	3.7	10.80	1080
	3:11	rest twelve minutes	....	84	13	193	118	144	4.3	176	4.8	7.15	1600
X. R. G., forty-four yr., female; body surface, 1.55 sq. m.	9:41	rest	....	60	4	255	115	156	2.5	132	4.3	4.75	2600
	9:52	rest	....	61	13	250	113	156	2.7	139	4.5	4.80	2580
	10:11	*l*-epinephrine eleven minutes	0.16	80	17	242	102	145	4.1	182	2.9	9.73	1180
	10:20	rest six minutes	....	74	13	229	98	138	3.3	154	3.8	6.27	1750
	10:47	rest thirty-three minutes	....	61	11	243	110	150	2.7	136	4.4	4.78	2490
XI. E. B., thirty-four yr., female; body surface, 1.54 sq. m.	9:57	rest	....	90	10	152	87	113	3.5	119	3.3	5.56	1608
	10:13	rest	....	90	9	152	88	113	3.5	121	3.8	4.93	1815
	10:32	*l*-epinephrine twelve minutes	0.11	108	12	150	79	106	4.3	153	2.6	9.04	928
	10:46	*l*-epinephrine twenty-seven minutes	0.20	119	12	155	79	107	4.7	171	2.6	10.10	842
	11:16	rest	....	104	11	132	74	94	3.8	139	3.2	6.67	846
	11:40	*l*-nor-epinephrine thirteen minutes	0.20	94	14	172	92	119	4.1	145	3.1	7.19	995

* Calculated as dry gas at 37°C. and 760 mm. barometric pressure.
† Corrected to 0°C. and 760 mm. barometric pressure.

after the infusion had been running eleven to twenty-two minutes. During the course of the experiments the patients received approximately 500 cc. of saline. During all but one of the cardiac output studies *l*-nor-epinephrine was used.

TABLE II

RANGE OF CHANGE OF CERTAIN CARDIOVASCULAR FUNCTIONS DURING REST AND THE INFUSION OF *l*-EPINEPHRINE AND *l*-NOR-EPINEPHRINE

Function	Fluctuation between Resting Values during Saline Infusion	Changes during Eleven to Fourteen Minutes of *l*-epinephrine Infusion in Doses of 0.15 to 0.30 μg./Kg./min.	Changes during Fifteen to Twenty-two Minutes of *l*-nor-epinephrine Infusion in Doses of 0.11 to 0.40 μg./Kg./min.	Changes after the Addition of Equal Amounts of *l*-epinephrine to *l*-nor-epinephrine Infusion
I. In eight normotensive patients				
	(8 cases)	(4 cases)	(8 cases)	(2 cases)
Systolic pressure mm. Hg	12 to 1	+60 to +18	+62 to +28	+12 to −19
Diastolic pressure mm. Hg	9 to 2	+12 to − 3	+25 to + 4	− 8 to −15
Mean systemic pressure mm. Hg	9 to 2	+22 to + 3	+37 to +14	− 4 to −17
Mean pulmonary arterial pressure mm. Hg	3 to 0	+10 to + 5	+19 to + 5	− 2 to − 6
Cardiac output L./min./sq. m. body surface	0.68 to 0	+4.23 to +2.56	+0.61 to −1.19	+2.23 to +2.42
Total peripheral resistance dynes cm^{-5} sec	234 to 36	−308 to −453	+825 to +62	−825 to −640
Pulse rate min	13 to 0	+16 to 0	+ 6 to −34	+25 to +10
II. In three patients with uncomplicated essential hypertension				
	(3 cases)	(3 cases)	(1 case)	
Systolic pressure mm. Hg	5 to 0	+20 to − 8	+40	
Diastolic pressure mm. Hg	2 to 1	+ 4 to −13	+18	
Mean systemic pressure mm. Hg	3 to 0	+ 8 to − 2	+25	
Mean pulmonary arterial pressure mm. Hg	1	+ 6 to + 3		
Cardiac output L./min./sq. m. body surface	0.41 to 0.03	+3.66 to +1.03	+0.34	
Total peripheral resistance dynes cm^{-5} sec	207 to 20	−422 to −973	+149	
Pulse rate min	2 to 0	+19 to +12	−10	

RESULTS

The full data obtained during the cardiac output studies on both groups of patients are summarized in Table I. The range of changes observed in the most significant cardiovascular functions of the two groups of patients during the initial period of rest and following the various drug infusions are presented in Table II. The data obtained during the preliminary nor-epinephrine infusion studies are summarized in Table III and the systolic pressure responses of the normal and hypertensive groups to different infusion rates of the drug are presented in Figure 2.

OBSERVATIONS OF PATIENTS WITH NORMAL BLOOD PRESSURE

Cardiovascular Response to Epinephrine Infusion. Upon intravenous infusion of epinephrine in doses of 0.15 to 0.30 μg./Kg./min. for a period of eleven to fourteen minutes the following hemodynamic changes were observed in four patients with normal blood

pressures: (1) A striking increase of cardiac output in all cases (78 to 98 per cent of the resting value); (2) a significant rise of the systemic systolic pressure associated with an insignificant change of the diastolic pressure in all cases; (3) a slight rise of the mean arterial pressure in three cases; (4) a sharp drop of the total peripheral resistance in every case; (5) a moderate rise of pulse rate in three cases and (6) a significant rise of the mean pulmonary arterial pressure.

The epinephrine infusion was continued at the same dosage for a thirty-seven-minute period in Case IV, at which time a further increase of the cardiac output and drop of the total peripheral resistance was noted. Furthermore, it is of interest that twenty-three minutes after termination of the epinephrine infusion and an appreciable time after the return of the systemic arterial pressures to normal limits an epinephrine effect was still present as judged by the persistent elevation of the pulse rate, oxygen consumption and cardiac output as well as by the lowered total peripheral resistance.

Comment. The cardiovascular response of the four subjects given an intravenous infusion of epinephrine was uniform and striking. It is evident that epinephrine, under the conditions of these experiments even with doses causing significant hypertension, acts as an overall vasodilator drug and a powerful cardiac stimulant. It should be noted, however, that the patients receiving the largest doses presented evidence of cutaneous vasoconstriction, i.e., pallor and a subjective sensation of cold.

TABLE III

RESTING LEVELS AND INCREASES OF SYSTEMIC ARTERIAL PRESSURES OBSERVED DURING *l*-NOR-EPINEPHRINE INFUSION IN A GROUP OF NORMOTENSIVE AND A GROUP OF HYPERTENSIVE PATIENTS

	Normotensive Group				Hypertensive Group			
	No. Cases	Mean	S.D.	Range	No. Cases	Mean	S.D.	Range
I. Resting Levels								
Systolic pressure mm. Hg	23	115	9.5	100–137	21	191	40.5	127–263
Diastolic pressure mm. Hg	23	70	7.7	54– 84	21	114	19.7	81–151
Mean pressure mm. Hg	23	85	7.9	73–100	21	139	25.3	96–179
II. Increase of Pressures with Increasing Doses of *l*-nor-epinephrine								
0.05–0.07 μg./Kg./min.								
Systolic pressure mm. Hg	12	8.4	6.0	0–23	21	30.0	19.5	0–65
Diastolic pressure mm. Hg	12	9.4	5.4	0–19	21	10.6	6.5	0–32
Mean pressure mm. Hg	11	7.3	3.4	0–13	21	16.7	10.1	0–43
0.10–0.13 μg./Kg./min.								
Systolic pressure mm. Hg	14	21.7	9.1	8–44	13	43.5	10.8	13–88
Diastolic pressure mm. Hg	14	13.6	7.0	4–25	13	17.3	8.3	5–34
Mean pressure mm. Hg	14	16.3	5.8	10–31	12	27.0	12.0	8–51
0.20–0.25 μg./Kg./min.								
Systolic pressure mm. Hg	14	38.0	9.0	6–56				
Diastolic pressure mm. Hg	14	22.0	8.6	5–34				
Mean pressure mm. Hg	14	26.5	11.2	5–42				

Cardiovascular Response to Nor-Epinephrine. In those preliminary experiments in which only the blood pressure and pulse rate were determined an increase of both diastolic and systolic systemic arterial pressures associated with a slowing of the pulse was noted. During the infusion of 0.05 to 0.07 μg./Kg./min. of nor-epinephrine there was

an average rise of systolic pressure of 8 mm. Hg; increasing the dose to 0.10 to 0.13 μg./Kg./min., the average rise was 22 mm. Hg; finally when 0.2 to 0.25 μg./Kg./min. was infused, the average rise of systolic pressure was 38 mm. Hg. (Table III, Fig. 2.)

The bradycardia appears to be of vagal origin since it was abolished by atropine in three cases. The relative lack of subjective symptoms even in the presence of high systolic pressures is noteworthy. The following hemodynamic changes were observed

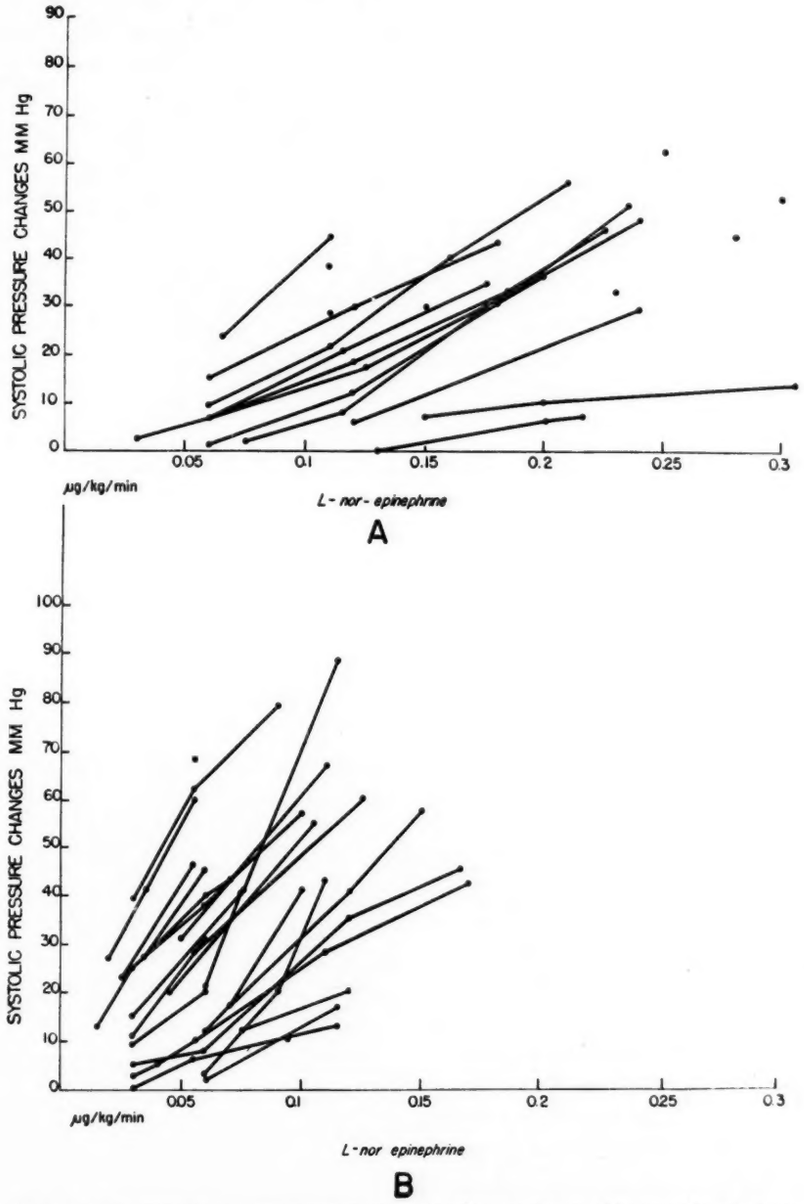


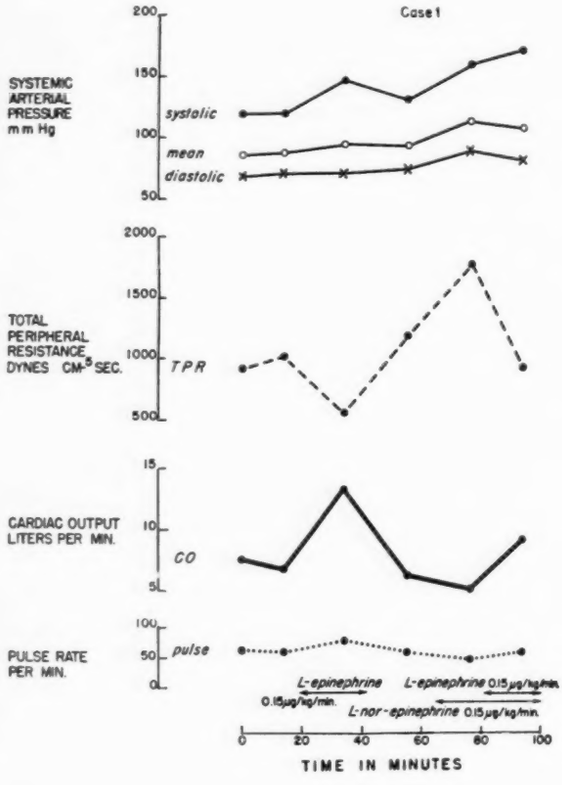
FIG. 2. The systolic pressure responses to increasing doses of *l*-nor-epinephrine: A, normotensive group; B, hypertensive group.

The minimum amount of nor-epinephrine required to produce a blood pressure elevation is variable in patients without cardiovascular disease but was on the average of 0.05 μg./Kg./min. (Table III.)

in eight subjects during the cardiac output studies following intravenous infusion of nor-epinephrine; in doses ranging from 0.11–0.40 μg./Kg./min. for a period of fourteen to twenty-two minutes: (1) An

unchanged or a moderate decrease of the cardiac output in seven cases. (The cardiac output of Case II rose by 18 per cent.) (2) A significant rise of systolic systemic arterial pressure in all cases associated with a significant rise of diastolic pressure in all cases. (3) A significant rise of the mean systemic arterial pressure in all cases. (4) A striking increase of total peripheral resistance in five cases. In no case was a drop observed. (5) A significant decrease of pulse rate in all but one case. (6) A significant rise of mean pulmonary arterial pressure in all cases.

In Cases V through VIII the nor-epinephrine infusion was continued for as long as twenty-nine to thirty-five minutes. In Case V in which the dosage was increased from a very low to a moderate amount no appreciable hemodynamic change was noted. In Cases VI through VIII in which the dosage was decreased an increase of cardiac output associated with relatively minor pressure changes resulted in a significant fall of the total peripheral resistance; this, however, did not reach resting values.



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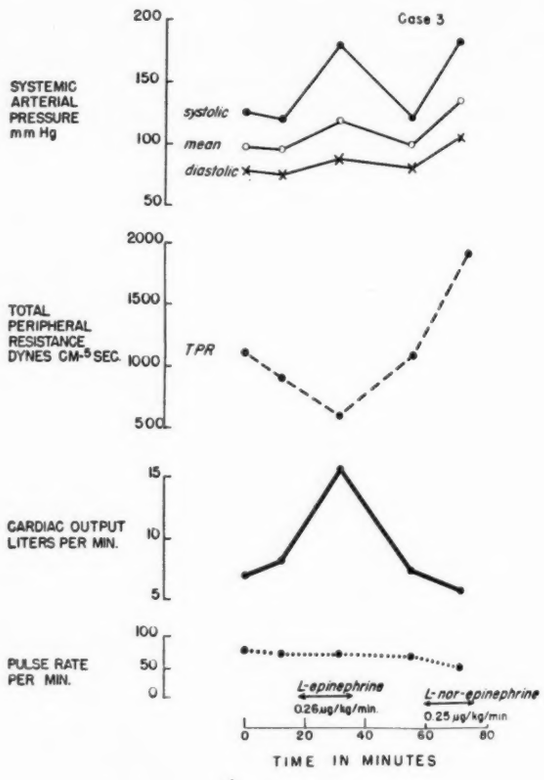

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FIG. 3. The hemodynamic changes observed in Case 1 during the successive infusion of *l*-epinephrine, *l*-nor-epinephrine and a combination of the two substances.

FIG. 4. The hemodynamic changes observed in Case 3 during the successive infusion of *l*-epinephrine and *l*-nor-epinephrine.

Cardiovascular Response to a Combination of Nor-Epinephrine and Epinephrine. In Cases I and II equal amounts of epinephrine were added to the nor-epinephrine infusion. The response to the combination of the two substances was: (1) a slight fall of mean arterial pressure; (2) a striking increase of cardiac output; (3) a sharp fall of the total peripheral resistance from the elevated levels during infusion of nor-epinephrine alone.

Two typical experiments are presented in Figures 3 and 4. Figure 3 represents the changes observed during rest and the successive infusions of equal doses of epinephrine, nor-epinephrine and a mixture of the two substances. During the infusion of 0.15 μg./Kg./min. of epinephrine the systolic pressure rose from 121 to 147 mm. Hg while the diastolic pressure remained unchanged. The cardiac output doubled and the total peripheral resistance fell from 1,030 to 577 dynes cm.$^{-5}$ sec., indicating an overall vasodilatation. Nor-epinephrine caused an increase of systolic and diastolic pressure from 133/76 to 162/91 mm. Hg, with a 17 per cent drop of cardiac output and a rise of total peripheral resistance from 1,205 to 1,785 dynes cm.$^{-5}$ sec., indicating an overall vasoconstriction. Finally, when equal amounts of epinephrine were added to the nor-epinephrine infusion, there was little change in blood pressure; the cardiac output increased from 5.18 to 9.22 L. per minute, and the total peripheral resistance dropped to 960 dynes cm.$^{-5}$ sec., indicating epinephrine—nor-epinephrine antagonism.

Figure 4 presents similar results obtained during a more significant hypertension induced by higher doses of the two substances. The infusion of a dose of 0.25 μg./Kg./min. of epinephrine caused a blood pressure rise from 120/75 to 180/87 mm. Hg, associated with an increase of cardiac output from 8.23 to 15.56 L. per minute and a drop of total peripheral resistance from 909 to 601 dynes cm.$^{-5}$ sec. The infusion of an equal amount of nor-epinephrine, which caused a blood pressure rise from 122/81 to 184/106 mm. Hg, was associated with a drop of cardiac output from 7.39 to 5.68 L. per minute and rise of total peripheral resistance from 1,090 to 1,915 dynes cm.$^{-5}$ sec.

Comment. From these findings the following conclusions may be drawn: (1) The primary action of nor-epinephrine is to produce an intense overall vasoconstriction and (2) this vasoconstriction action is completely blocked by the simultaneous administration of equal doses of epinephrine.

This antagonistic action of epinephrine to the nor-epinephrine effect amply explains the less uniform cardiovascular response of the patients to a small dose of nor-epinephrine. In such complicated experiments, necessitating the presence of five or six observers and a considerable amount of equipment, it may be impossible to prevent some patients from experiencing mild anxiety. The hemodynamic response to anxiety, as Hickam and his co-workers[22] have recently shown, is in some cases similar to that obtained with small doses of epinephrine. Likewise, the observation of a moderate increase of cardiac output and consequent lowering of the peripheral resistance after a prolonged period of nor-epinephrine infusion, as seen in Cases VII and VIII, may be ascribed to the release of endogenous epinephrine in response to the prolonged procedure.

Epinephrine and nor-epinephrine resemble one another superficially by producing an increase of systolic and mean arterial pressures. Nor-epinephrine hypertension, however, is due to an increase of total peripheral resistance with no significant change or even a drop in cardiac output whereas epinephrine hypertension is the result of a significant increase of cardiac output in spite of a decrease of total peripheral resistance. These findings are demonstrated graphically in Figure 5. Finally, the vasoconstrictor action of nor-epinephrine can be blocked entirely by the simultaneous administration of equal amounts of epinephrine.

In normal subjects nor-epinephrine produces a type of hypertension that closely resembles that of essential hypertension. Both are characterized by a proportionate increase of systolic and diastolic pressure and by lack of tachycardia and of subjective symptoms. The uniform increase of total peripheral resistance is the only outstanding abnormality in both.

Nor-epinephrine hypertension is similar in its hemodynamics to the acute hyper-

tension produced by neosynephrine[23] and paredrinol.[34] It is noteworthy that Stead and Kunkel[34] who carefully studied paredrinol hypertension were impressed by its similarity to essential hypertension. There is no evidence, however, that these substances occur naturally. Since an increase of stroke volume was observed, it may be concluded that the decrease of cardiac output is due to regulating mechanisms such as bradycardia rather than to cardiac failure. In one case the right auricular pressure was measured and found to be normal during nor-epinephrine administration.

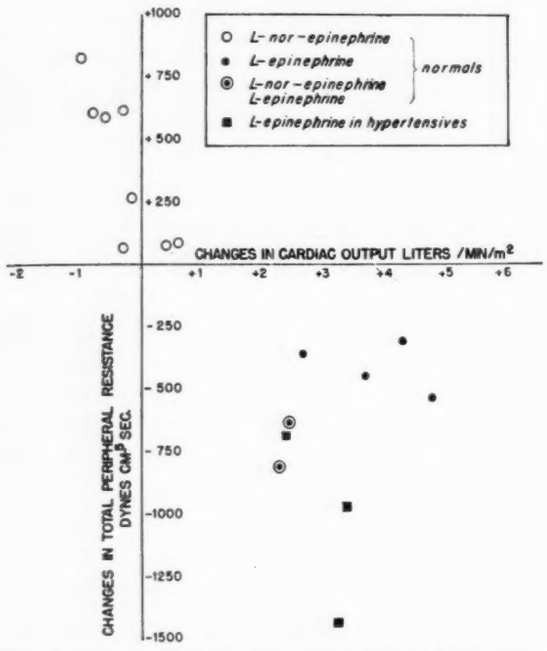


FIG. 5. The correlation between changes in cardiac index and changes in total peripheral resistance during the infusion of *l*-epinephrine and *l*-nor-epinephrine found in eight normotensive and three hypertensive patients.

Epinephrine, on the other hand, in a range of dosage comparable to the physiologic release was found to be an overall vasodilator. Generalized vasoconstriction in man, however, has been observed in patients with pheochromocytoma,[19] a condition in which large amounts of circulating epinephrine are present. This type of response resembles the intense vasoconstriction commonly observed in animal experiments as indicated by the diminished volume of organs. A hypotensive action of epinephrine following minute doses has been described[8,28] but was not considered to have physiologic significance. Although the actual doses given in our experiments appear small, it is well known that man is more sensitive to epinephrine than laboratory animals. These doses, which were within and even beyond the physiologic range as shown by the marked pressor response, produced vasodilatation.

From our data it is impossible to state the site of epinephrine vasodilatation. Examination of the data of Allen et al.[1] indicates that the increase of blood flow is not confined to the muscles. There are three possible mechanisms by which epinephrine may cause vasodilatation: (1) direct action on the arteriolar muscle;[10] (2) blocking of transmission through the sympathetic ganglia;[7,26] (3) an epinephrine-nor-epinephrine antagonism. A depression of ganglionic transmission by epinephrine has only been observed following single massive doses.[7] In fact during epinephrine infusion facilitation of ganglionic transmission has been reported.[7] The demonstration in our experiments of an epinephrine-nor-epinephrine antagonism indicates that sympathetic tone, insofar as mediated by nor-epinephrine, may be abolished by epinephrine. This view makes it possible to reconcile the predominantly vasodilator response to epinephrine of unanesthetized man with the constrictor action seen in the vast majority of animal experiments and in cases of pheochromocytoma.

The increase of the mean pulmonary arterial pressure during epinephrine and during nor-epinephrine infusions is of great interest. It is impossible to decide from the data obtained in the present study whether this increase is due to back pressure from an elevated left auricular pressure or to vasoconstriction of the pulmonary vascular bed. Although a rise of left auricular pressure in dogs had been previously reported following large doses of epinephrine,[21] recent animal experiments[14,25] indicate that the left auricular pressure may not increase

following an injection of either substance and that the rise of pulmonary arterial pressure may be on the basis of vasoconstriction.

OBSERVATIONS ON PATIENTS WITH UNCOMPLICATED ESSENTIAL HYPERTENSION

Although only a limited number of patients with essential hypertension were studied, the results are so consistent that a preliminary report may be of interest.

Cardiovascular Response to Intravenous Infusion of Epinephrine. During the intravenous infusion of epinephrine in doses of 0.07 to 0.20 μg./Kg./min. for a period of ten to twenty minutes the following hemodynamic changes were observed in three patients with essential hypertension: (1) A significant rise of the cardiac output in all cases; (2) a fall of the systolic and diastolic systemic pressure in two cases and an insignificant rise in one; (3) a fall of the mean arterial pressure in all cases; (4) a profound drop of the total peripheral resistance in all cases; (5) a significant rise of pulse rate in all cases; (6) a significant rise of the mean pulmonary arterial pressure in all cases.

Comment. From these limited observations it would seem that the hemodynamic response to epinephrine infusion of the hypertensive patients differs from that of the normotensive patients in the following respects: (1) A greater sensitivity to the vasodilator action of epinephrine characterized by a very marked lowering of the total peripheral resistance and (2) a tendency for the systemic arterial pressure to fall or remain relatively constant.

The striking similarity of this response with the epinephrine response of the normal group made hypertensive with nor-epinephrine should be noted. Furthermore, in Case XI twenty-four to forty-six minutes after stopping the epinephrine infusion, although the cardiac output had returned toward normal, a lowered peripheral resistance and a nor-epinephrine antagonism could be demonstrated. The results of the observations on the three patients are presented in Figures 6 to 8.

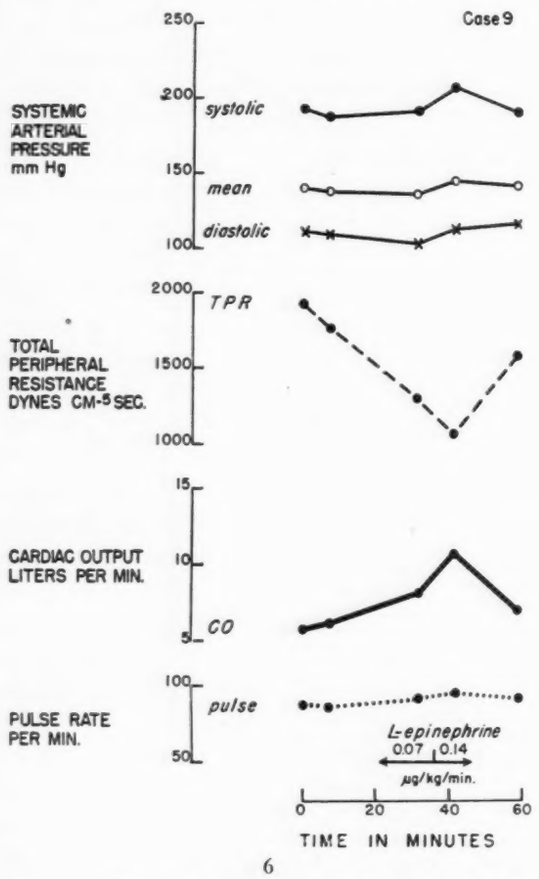
Cardiovascular Response to the Infusion of Nor-Epinephrine. During the nor-epinephrine sensitivity tests fourteen patients with uncomplicated hypertension showed an increased response of the systolic and mean arterial pressures when compared with the normotensive group. The diastolic pressure changes did not differ from the normal group. (However, during anesthesia an increased response of the diastolic pressure was observed in eight hypertensive patients.) In addition, normal responses were observed in two patients with essential hypertension tested at a time when their blood pressure was normal, one patient with chronic nephritis, one with cardiac failure due to hypertensive cardiovascular disease and one with generalized arteriosclerosis and hypertension. As may be seen in Figure 2 if dosage is plotted as abscissae and systolic blood pressure changes as ordinates, the concentration action curves of the hypertensive patients are shifted to the left of and show a steeper slope than those of the normotensive group. This increased sensitivity of the hypertensive patients obviously limited the dose administered. Although the groups are small, there is a statistically significant difference between the mean rise of the systolic and mean pressures of the two groups. (Table III.) The apparent decrease of the difference between the two groups with a dose of 0.1 to 0.13 μg/Kg./min. may be due to the fact that the most sensitive hypertensive patients did not receive this higher dose. Observations made on hypertensive patients during anesthesia, however, when the blood pressure was at a low level, showed them also to be more sensitive to large doses. The reflex slowing of the pulse due to blood pressure rise was less apparent and sometimes completely lacking in hypertensives.

Comment. From these limited observations it would appear that hypertensives are more sensitive to nor-epinephrine than normotensive subjects.

The blood pressure concentration action curves obtained in normals and hypertensives resemble ascending limbs of hyper-

bolae.* The difference in sensitivity to nor-epinephrine between normals and hypertensives is significant, judged both from the curves and the statistical analysis.

It is possible that the increased sensitivity of hypertensives to nor-epinephrine is due to the lack of an antagonistic factor, epinephrine, in the peripheral nerve endings. This is analogous to the shift in concentration action curves for a mixture of epinephrine and its antagonist, ergotamine, as compared with the curves for epinephrine alone.[16]



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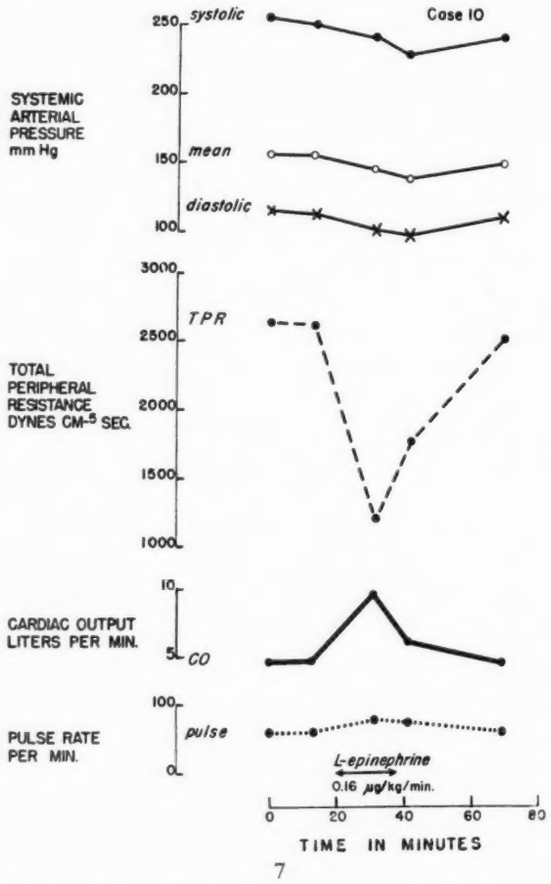

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FIG. 6. The hemodynamic changes observed in Case 9 during the infusion of *l*-epinephrine.
FIG. 7. The hemodynamic changes observed in Case 10 during the infusion of *l*-epinephrine.

COMMENTS

From these experiments it is tempting to develop the hypothesis that nor-epinephrine plays an important rôle in the mechanism of essential hypertension. If nor-epinephrine is the "mediator" of essential hypertension, its site of release is confined to the sympathetic nerve endings. The fact that nor-epinephrine infusion causes an increase of pulmonary arterial pressure whereas in uncomplicated essential hypertension the pulmonary pressure values are normal[6] casts doubt upon the view that nor-epinephrine is present in significant amounts as a circulating agent.

Two possible mechanisms of transmission remain: (1) an increase of sympathetic tone in areas where nor-epinephrine is the mediator, producing vasoconstriction or (2) an excess of nor-epinephrine due to failure of methylation or lack of methyl donors. The second possibility assumes that normal sympathetic activity is due to the presence of both epinephrine and nor-

* No concentration action curves derived from animal experiments are available for nor-epinephrine but they can be expected to obey the same laws as those for epinephrine or acetylcholine and to give rectangular hyperbolae.[9,32,41] This is true for excitor and inhibitor actions as well.

epinephrine in varying amounts as suggested by Bacq.[3] Thus, essential hypertension might be considered to be a metabolic disease of deficient transmethylation although no definitive evidence is provided by the present study.

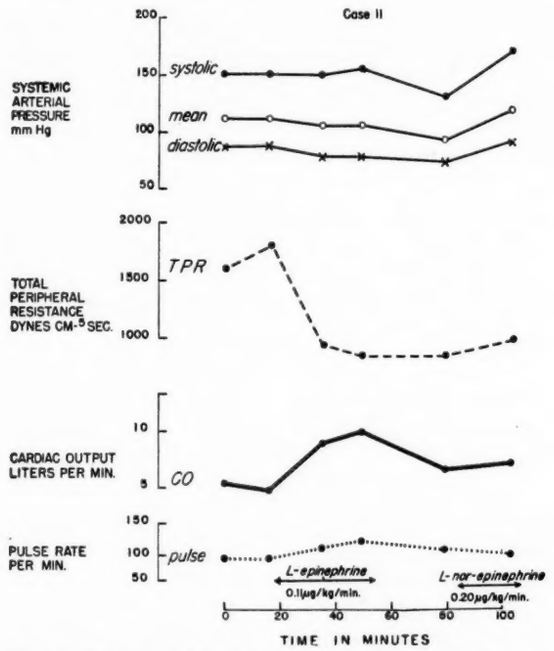

FIG. 8. The hemodynamic changes observed in Case II during the successive infusion of *l*-epinephrine and *l*-nor-epinephrine.

SUMMARY AND CONCLUSIONS

Using the technic of right heart catheterization, eight normotensive and three hypertensive patients were studied during the infusion of varying doses of epinephrine, nor-epinephrine and a mixture of the two substances. Direct measurements made included the cardiac output by the direct Fick method and the simultaneous recording by Hamilton manometers of the systemic and pulmonary arterial pressures. In addition, the systemic blood pressure and pulse rate of twenty normotensive and sixteen hypertensive patients were followed during similar infusions. Epinephrine, in doses sufficient to cause significant hypertension, was found to act as an overall vasodilator as well as a powerful cardiac stimulant. The hemodynamic response of the hypertensive patients to epinephrine differed from that of the normal subject quantitatively rather than qualitatively. It was characterized both by a marked lowering of the total peripheral resistance to normal levels and frequently by a fall of the systemic arterial pressure. The primary action of nor-epinephrine was intense vasoconstriction. No significant cardiac action was observed in the range of dosage employed. This vasoconstrictor action was completely blocked by the synchronous administration of equal doses of epinephrine. Nor-epinephrine produced a type of hypertension that closely resembled essential hypertension. Patients with essential hypertension showed an increased pressure response to nor-epinephrine as contrasted with normotensive subjects. It is possible that this increased sensitivity is due to the lack of an antagonistic factor, epinephrine, in the peripheral nerve endings. Our findings are compatible with the concept that nor-epinephrine is a sympathetic mediator of overall vasoconstriction and suggest that a disturbed balance between both "sympathetic transmitters" could be concerned in the production of hypertension. The mean pulmonary arterial pressure was increased by the infusion of both substances, but it was impossible to decide from our own data whether this increase was due to back pressure from an elevated left auricular pressure or to vasoconstriction of the pulmonary vascular bed.

The authors gratefully acknowledge the technical assistance of Miss Thelma L. Berg, Miss Theodora J. Lannon, Miss Estelle M. Schechter and Miss Katherine Vislocky and the helpful criticism of Dr. Alfred Gilman and Dr. George A. Perera. The *l*-nor-epinephrine was supplied to us through the generosity of Dr. M. L. Tainter.

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Effect of Tetraethylammonium in Arterial Hypertension*

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In previous reports we[1-3] have described the pharmacologic effects of tetraethylammonium ion (TEA) in normal and hypertensive subjects and in persons with arteriosclerotic vascular disease. Our results on the whole coincide with those obtained by the group at the University of Michigan[4-6] except that we found the vasodilator effect of TEA to be inferior to that produced by local nerve and paravertebral block. Similar results have since then been published by others.[7] In our first paper[1] we suggested that TEA might be of value as a preoperative test in hypertension for the purpose of selecting patients suitable for lumbodorsal sympathectomy. Such studies have also been carried out by others.[8-11]

The purpose of the present investigation was to study the effect of a standardized dose of TEA on a larger group of patients with hypertension, divided according to age and height of blood pressure, and to compare the effect of TEA upon blood pressure with the spontaneous variability of blood pressure during rest. We have also studied the influence of TEA on the pressure in the right auricle and ventricle and the pulmonary artery, its effect on cardiac output determined according to the direct Fick principle and its effects on the mean systemic pressure by intra-arterial registration.

MATERIAL AND METHODS

Seventy-one patients with hypertension were studied. Their ages varied between nineteen and seventy years. All patients were hospitalized and in all of them the following examinations were carried out: Spontaneous variation in blood pressure recorded during standardized serial determinations (twenty-four-hour recordings),[12] eyeground examination and complete examination of the heart and kidneys. The highest systolic pressure varied between 160 and 270 and the highest diastolic pressure between 100 and 170 mm. of mercury.

The test dose consisted of 5 mg. of TEA per Kg. of body weight administered intravenously. This dose was chosen because we[3] have noted that a larger dose of TEA may be dangerous in angina pectoris and in hypertension in patients with marked generalized arteriosclerosis, whereas a dose of 5 mg. may be considered safe. In nineteen cases we have compared the effect of a dose of 5 mg. and of 10 mg. of TEA in the same patient.

All patients were in the recumbent position when the test was performed. Before the injection blood pressure and pulse rate were recorded several times until constant levels were obtained and this was repeated every minute after the injection until the blood pressure started to rise again, i.e., for ten to twenty minutes. The lowest pressure and the maximum change in pulse rate registered after the injection were used in the calculation of the effect of TEA.

The technic of heart catheterization and pressure registration has recently been described.[13]

RESULTS

The individual response to a standardized dose of TEA showed great variations even in cases which were clinically similar. No statistically proved difference between vari-

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ous groups of hypertensive patients could therefore be demonstrated. When the material was divided according to age and to height of blood pressure, however, there were some differences. As seen in Table I the mean drop in both systolic and diastolic pressure was greater in patients with a higher initial pressure elevation than in subjects with a lower elevation. This is in accordance with the results of Lyons et al.[10] They found that the mean decrease in diastolic pressure after administration of TEA increases with increasing initial diastolic elevation. The effect upon the pulse rate was about the same in patients with a great or slight increase in blood pressure. (Table I.)

TABLE I

EFFECT OF TEA IN HYPERTENSIVE PATIENTS CLASSIFIED ACCORDING TO BLOOD PRESSURE LEVEL

Blood Pressure before TEA	No. of Cases	Blood Pressure before TEA Mean	Effect of 5 mg. of TEA/Kg. of Body Weight Administered Intravenously			
			Drop in Blood Pressure (mm. Hg)		Change in Pulse Rate (beats per min.)	
			Mean	Limits	Mean	Limits
Systolic						
145–195	34	173	37	5–75	+17	−12 + 36
>200	34	220	56	5–130	+15	−16 + 44
Total	68	197	47	.....	+16	
Diastolic						
90–105	16	99	13	0–30	+15	0 + 36
110–130	33	115	24	0–50	+18	−12 + 36
>135	19	140	29	0–60	+13	−16 + 44
Total	68	118	23	.....	+16	

In Table II the extent of the fall in blood pressure after TEA is compared with the spontaneous pressure variations at rest. The average decrease in pressure after TEA on the whole coincides with the spontaneous variability. In hypertensive patients with a systolic pressure lower than 200 mm. of mercury and a diastolic lower than 110 the lowest pressure obtained after TEA agrees with the lowest spontaneous value. In subjects with a higher elevation in the blood pressure TEA causes a fall in pressure below the lowest spontaneous value. The pulse pressure thus is diminished to a greater extent in patients with a higher pressure elevation. In spite of this the increase in pulse rate after TEA is about the same for the different groups.

In Table III the patients are arranged according to age. After administration of TEA the average fall in systolic pressure was least in the youngest group and greatest in the oldest. The reduction in pulse pressure was also most pronounced in the oldest group. The effect upon the pulse rate was the opposite, the youngest patients showed the greatest increase and the oldest the lowest. On the whole, the spontaneous variations in blood pressure were the same for all groups.

TABLE II

COMPARISON BETWEEN THE EFFECT ON BLOOD PRESSURE OF 5 MG. OF TEA/KG. OF BODY WEIGHT ADMINISTERED INTRAVENOUSLY AND THE SPONTANEOUS VARIABILITY OF BLOOD PRESSURE IN SIXTY-EIGHT HYPERTENSIVE CASES

Blood Pressure before TEA	No. of Cases	Drop after TEA (mm. Hg) Mean	Difference between Highest and Lowest 24-hr. Readings Mean	Lowest Pressure after TEA Mean	Lowest Pressure at 24-hr. Reading Mean
Systolic					
145–195	34	37	50	136	138
>200	34	56	52	164	180
Total	68	47	51	150	159
Diastolic					
90–105	16	13	24	86	84
110–130	33	24	31	91	94
>135	19	29	28	111	116
Total	68	23	29	95	96

The older patients showed the highest initial elevations in blood pressure. In the preceding pages we have shown that the extent of the pressure fall increases with increasing initial elevation. It is therefore possible that the differences in the pressure drop for the various age groups were due to different heights of initial elevation. In order to ascertain if the differences in the decrease in pressure between the various

age groups depended on different heights of initial elevation each of the three groups was divided into two subgroups. (Table III.) The first subgroup (A) includes the patients showing a greater fall in systolic pressure than the average, the second sub-group (B) patients showing a smaller decrease. Within each age group no difference in the initial pressure elevation could be demonstrated for the two subgroups. The different effects of TEA in the various age groups therefore cannot be explained by differences in the initial pressure elevation. In the two youngest age groups the mean increase in pulse rate for the corresponding subgroups was the same.

The patients in the oldest age group showing the greatest fall in systolic pressure

TABLE III

EFFECT OF 5 MG. OF TEA/KG. OF BODY WEIGHT ADMINISTERED INTRAVENOUSLY IN SIXTY-EIGHT HYPERTENSIVE PATIENTS CLASSIFIED ACCORDING TO AGE

	No of Cases	Blood Pressure before TEA (mm. Hg)		Effect of TEA			Highest Pressure at 24-hr. Readings (mm. Hg)		Difference Between Highest and Lowest 24-hr. Readings (mm. Hg)	
				Drop in Blood Pressure (mm. Hg)		Change in Pulse Rate Beats/min.				
		Systolic	Diastolic	Systolic	Diastolic		Systolic	Diastolic	Systolic	Diastolic
Group I: younger than 45 yr.	20									
Mean	..	176	116	36	23	+24	195	123	47	24
Group II: 45 to 55 yr.	32									
Mean	..	202	121	47	24	+18	215	129	40	27
Group III: older than 55 yr.	16									
Mean	..	206	115	52	13	+ 9	225	133	48	31
Age groups classified according to systolic drop in blood pressure after TEA*										
Group I:										
A	8									
Limits	..	170–190	100–135	40–85	10–50	+12 +36	160–240	110–140	25–90	5–40
Mean	..	179	115	54	29	+23	194	131	41	21
B	12									
Limits	..	150–210	100–140	5–35	0–25	+ 8 +42	170–240	100–160	25–90	5–45
Mean	..	174	117	23	13	+25	196	118	53	26
Group II:										
A	15									
Limits	..	140–250	90–160	50–85	15–45	−16 +40	180–270	90–160	10–85	15–40
Mean	..	210	127	65	30	+18	223	129	38	24
B	17									
Limits	..	145–235	90–150	20–45	10–30	−12 +44	160–250	100–160	20–75	15–45
Mean	..	196	116	34	19	+18	208	129	42	30
Group III:										
A	7									
Limits	..	190–225	110–155	70–130	25–60	− 4 +24	215–270	120–160	35–70	20–50
Mean	..	216	126	87	41	+6	242	143	60	39
B	9									
Limits	..	170–240	95–120	5–60	0–30	0 +36	165–270	105–170	25–55	20–30
Mean	..	198	105	35	12	+11	200	127	36	26

* Subgroups A include those patients in whom the systolic drop after TEA is greater than the average drop and those in group B in whom the systolic drop is less than the average in the various age groups.

and the largest reduction in pulse pressure also showed the least rise in pulse rate. In this group the vascular changes were the most pronounced clinically.

Nineteen of the patients were on different occasions given both a dose of 5 mg. and 10 mg. of TEA per Kg. of body weight. Their ages varied between thirty-three and seventy years. Only the lowest pressure and the maximum change in pulse rate obtained after the two various doses of TEA were used for comparison of the effect in order to eliminate the error involved in different initial levels of pressure and pulse rate. After a dose of 10 mg. the systolic pressure was an average of 22 ± 19.2 mm. of mercury and the diastolic 12 ± 10.8 mm. lower than when a dose of 5 mg. was given. The large mean errors show the great individual differences in the effect of the doses. As shown by Levinson et al.[14] there are considerable daily fluctuations in both the magnitude of the depressor response and the blood pressure floor in serial injections of TEA in hypertensive subjects. Such fluctuations may contribute to the individual differences in response to various dosages of TEA.

In several patients, especially those with mild hypertension, there was no difference in effect between the larger and smaller dose. Ten of the patients were younger than fifty years. In these patients the average fall in systolic and diastolic pressure after a dose of 10 mg. was, respectively, 17 mm. of mercury and 10 mm. greater than when 5 mg. was administered. In the nine patients over fifty years of age the corresponding figures were 29 mm. systolic and 14 mm. diastolic. In these patients, in spite of the greater fall in pressure after 10 mg. of TEA, the pulse rate with this dose was on the average nine beats slower than after 5 mg. In the younger patients there was an average rise in the pulse rate of five beats per minute when the dose of TEA was doubled. The differences in the effect of TEA for different age groups of hypertensives thus

TABLE IV

EFFECT OF TEA (5 MG./KG. OF BODY WEIGHT) ON BLOOD PRESSURES, CARDIAC OUTPUT AND VASCULAR RESISTANCE IN A YOUNG PATIENT WITH ARTERIAL HYPERTENSION

Case K.P. 21 yr.	Before TEA	After TEA					
		30 sec.	3 min.	9 min.	17 min.	25 min.	50 min.
Blood pressure: brachial artery							
systolic	256	217	174	192	210	205	236
diastolic	139	120	101	112	121	120	132
mean	189	160	129	143	154	153	175
Blood pressure: pulmonary artery							
systolic	23	...	13	14	16	16	
diastolic	9	...	6	4	6	6	
mean	13	...	9	8	10	10	
Blood pressure: right ventricle							
systolic	30	37	...	...	21	28	
diastolic	−0.4	−0.8	...	...	−0.4	1.5	
mean	9	11	...	...	6	8	
Heart rate per min	111	136	118	100	107	102	100
A-V oxygen difference, cc./l	31	...	42	...	38	37	
Cardiac output, l/min	6.98	...	5.38	...	5.94	6.1	
Stroke volume, cc./beat	63	...	46	...	55	60	
Peripheral resistance	2.162	...	1.920	...	2.070	1.985	
Pulmonary resistance, $\frac{\text{dynes seconds}}{\text{centimeter}^5}$	154	...	134	...	140	112	

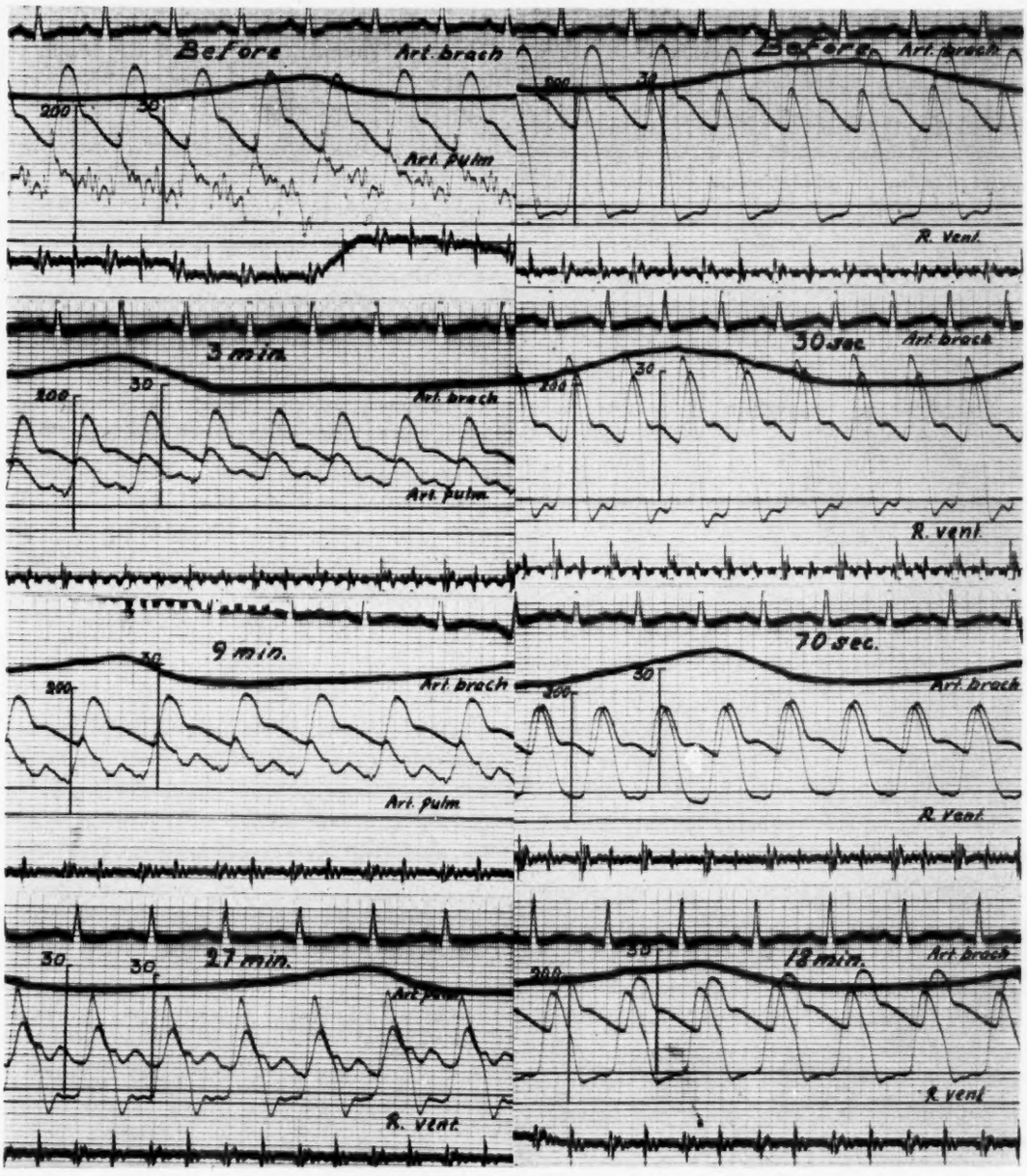

FIG. 1. A and B, the effect of 5 mg. TEA/Kg. of body weight on the blood pressures in the brachial artery, pulmonary artery and right ventricle in a young hypertensive woman. In each section from above down E.C.G. lead II, respiration, brachial arterial pressure, pulmonary arterial or right ventricular pressures and phonocardiogram; standards in mm. Hg. The demonstrated records were taken before, and thirty and seventy seconds, three, nine, eighteen and twenty-seven minutes after the administration of TEA. Note the initial increase in systolic and decrease in diastolic pressure in the right ventricular pressure curve.

became more marked with larger doses. This also demonstrates the risk of giving large doses of TEA to older and arteriosclerotic patients as previously pointed out.[3]

In three patients with arterial hypertension between twenty-one and forty years of age the influence of TEA on the cardiac output and the pressure in the lesser circulation was studied. Table IV and Figure 1 show the figures obtained in one case. The results were similar in the two other cases studied. Immediately after the intravenous injection of 5 mg. per Kg. of body weight the systemic blood pressure decreased and the

pulse rate increased. With the increase in pulse rate, there was a slight rise in the systolic pressure in the right ventricle, followed by a decrease. There was a slight decrease in cardiac output three to thirty minutes after the administration of TEA. The end diastolic (filling) pressure in the right ventricle first decreased, then increased to a value higher than the original pressure. The changes in the peripheral vascular resistance were not of the same magnitude as the blood pressure fall due to the changes in cardiac output. The relatively larger fall in blood pressures in the lesser circulation as compared with the systemic circulation indicates a shift of the blood volume toward the peripheral blood vessels.

COMMENTS AND CONCLUSIONS

The decrease in arterial pressure occurring after administration of TEA is caused by ganglionic blockade of the sympathetic nervous system resulting in vasodilatation.[1,4,5,10] The increase of the pulse rate may be explained either as a compensatory rise in the heart rate in order to counteract the effect of the fall in blood and pulse pressures on the cardiac output or as a direct effect upon the autonomic innervation of the heart.

In younger hypertensive patients without pronounced vascular changes TEA causes a moderate drop in both the systolic and diastolic pressures corresponding to the lowest spontaneous value obtained during rest and sleep. In these patients TEA produces the relatively greatest increase in the pulse rate. Therefore, in this group of patients no greater decrease in the cardiac output should be expected. Our three patients, in whom the influence of TEA upon cardiac output was studied by means of the direct Fick principle, were all under forty years of age and all showed a very slight decrease in the cardiac output. There was a marked lowering of the pressure in the lesser circulation, about one-half of the basic value. This decrease in the pressures was maintained for a considerably longer time than in the peripheral circulation and probably is not due to the direct influence of TEA on the innervation of the lesser circulation. This innervation plays an uncertain rôle in regulation of the pressure in the lesser circulation.[15] Furthermore, our patients showed an initial increase in the pressure coincident with the rise in pulse rate. The probable explanation of this decrease is that a larger part of the blood volume, because of lessening of the constriction, has been located peripherally. This agrees with the increase in vital capacity observed after administration of TEA to hypertensive subjects.[9] The vasodilator effect of TEA lasts longer than the decrease in blood pressure. This fact explains why the fall in pressure in the lesser circulation is sustained over a longer period than in the systemic circulation.

Reiser and Ferris[16] have shown that the cold pressor response in hypertensives is eliminated after the administration of TEA. Larsson[17] has demonstrated the essential importance of peripheral vascular tone for the magnitude of the cold pressor response under the influence of TEA. Reiser and Ferris found a delayed cold pressor response in some hypertensives. They refer this delayed effect to a humoral mechanism. Such a suggestion is hardly justified as a delayed cold pressor response could be caused by anxiety. Hammarström[12] has pointed out that centrally acting factors contribute to differences in action of a neurogenic reflex such as the cold pressor response. These factors may also influence the depressor effect of TEA.

In older hypertensive patients with clinical signs of arteriosclerotic changes TEA produces the greatest drop in systolic pressure and relatively the least fall in diastolic pressure. In these cases the decrease in blood pressure after administration of TEA falls below the lowest spontaneous value. The reduction in pulse pressure is greatest in this group and these patients also show the lowest average increase in the pulse rate after the injection of TEA. In some cases there was a slowing of the heart rate. Thus if administration of TEA to a patient

with hypertension produces a noticeable fall in the systolic pressure and a relatively moderate drop in the diastolic pressure simultaneously with a slight increase or decrease in the pulse rate, this is a sign of arteriosclerotic changes. This was strikingly demonstrated by the patient showing the greatest systolic drop after TEA in our series. This man, seventy years of age, had advanced cardioarteriosclerosis and died two months after the TEA test from a rupture of the abdominal aorta. After injection of 5 mg. of TEA per Kg. of body weight the blood pressure fell from 255/155 to 125/90 while the pulse rate varied between 96 and 92 beats per minute.

The degree of reduction in blood pressure after lumbodorsal sympathectomy in hypertension does not run parallel either with the spontaneous variability of the blood pressure or the drop in pressure obtained in preoperative tests with amytal and nitrite.[12] Hammarström[12] found that the lowest blood pressure obtained after amytal agreed in all groups of hypertensives with the lowest spontaneous value. Administration of nitrite to patients with mild hypertension produced a decrease to the lowest spontaneous value whereas in those with more marked vascular changes the blood pressure fell below this level. The effect of a standardized dose of TEA upon the blood pressure thus agrees best in various hypertension groups with the effect obtained after nitrite administration. The various groups of hypertensive patients in Hammarström's series agree well with the groups in this present series, with respect to age, average height of blood pressure and degenerative vascular changes. A comparison of the effect of nitrite and of TEA indicates that in cases with vascular changes TEA produces a larger fall in systolic pressure and a greater reduction in pulse pressure than nitrite.

Conflicting opinions have been expressed regarding the value of TEA as a preoperative test for sympathectomy in hypertension.[8–11] With the exception of Lyons et al.,[10] the different points of view have been based upon results in small series of patients. The results of Lyons et al.[10] show that poor response of the diastolic pressure to TEA indicates a poor result of sympathectomy. On the other hand, a good response of the diastolic pressure did not guarantee a favorable effect from the operation. Our results show that it is possible even in this latter group to select patients suitable for operation if consideration is taken not only of the fall in diastolic pressure but also of the change in pulse rate and pulse pressure. A marked drop in systolic pressure and a great reduction in pulse pressure with little or no increase in pulse rate after administrations of TEA indicates advanced degenerative changes associated with hypertension. According to clinical experience, sympathectomy is of less value in these cases.

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Effect of the Low Sodium Diet and the Rice Diet on Arterial Blood Pressure*

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INTEREST in the dietary treatment of hypertension has recently been stimulated by the work of Kempner,[1] Grollman,[2] Perera[3] and others.[4,5] In much of the previous work on the effect of diet on hypertension the control periods were not adequate. Schroeder[6] reviewed the literature on the low sodium diet in essential hypertension and pointed out the importance of sufficiently long control periods in judging the effects of any therapeutic measure in this disease. This report is based upon our observations of a group of hypertensives who were followed over a prolonged period prior to and after the introduction of dietary therapy. Because the proponents of the rice diet claim specific virtues for that diet, a comparison was made between the rice diet and a diet low in sodium but adequate in protein.

METHODS

Nine patients with essential hypertension, three females and six males ranging in age from thirty-two to fifty-nine, were studied. Two of the nine patients had impairment of renal function but no nitrogen retention. There was no evidence of primary renal disease nor of cardiac failure.

All nine patients were hospitalized throughout the period of study. Each patient was studied in a control period averaging one month directly prior to the institution of dietary therapy. In this period they were on the ward diet containing approximately 2,100 calories and 6 Gm. of sodium chloride. Estimation of arterial blood pressure was made twice daily under the same conditions, urinary output was recorded and frequent determinations of blood and urinary sodium were made with a flame photometer.* Blood pressure determinations were made by two observers, in the morning with the patient recumbent and in the afternoon with the patient up and about. After the control period the patients were placed on the dietary regimen for not less than four weeks. The low sodium diet provided 1,800 calories, 70 Gm. of protein and 300 mg. of sodium. The rice diet contained 2,000 calories, 20 Gm. of protein and 150 mg. of sodium. While the patients were on this restricted diet, the same observations were made as during the control period but more frequent determinations of urinary sodium were made to assure ourselves that the patients were adhering to the diet. Seven patients were studied on the low sodium diet; of these four received the rice diet in addition. One patient had the rice diet alone and one was dropped from the study when it was found he was not adhering to the diet.

The blood pressure values recorded in the following tables represent the average of the last ten days of measurements during each dietary period. The average of the last ten days of each period was chosen since it was thought this represented the maximum effect of diet. The standard errors of the means of these values is in the order of plus or minus 3. The differences were subjected to analysis by Fisher's t test.

RESULTS

In two of the patients, H. H. and R. S., there was a fall in plasma sodium level while on the rice diet but a comparable fall did not occur on the low sodium diet. In

* Sodium determinations were done by Dr. Robert Berliner of the Columbia University Research Service, Goldwater Memorial Hospital.

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patients G. M. and L. N. a significant fall in plasma sodium level occurred while they were on the low sodium diet. (Table I.) In all patients the urinary sodium excretion fell to very low levels on both diets, but the levels on the rice diet were somewhat lower than on the low sodium diet. This was attributed to the lower sodium content of the rice diet. This fall in urinary sodium generally occurred from the third to the seventh day of dietary restriction.

All of the patients on the restricted diets experienced a weight loss ranging from 4½ to 14 pounds. The weight was regained

TABLE I

DATA ON REGULAR, LOW SODIUM AND RICE DIETS: PLASMA AND URINE SODIUM LEVELS AND AVERAGE ARTERIAL BLOOD PRESSURE READINGS

Case	Diet	Sodium		Blood Pressure		Duration of Period	Weight
		Blood*	Urine†	Systolic	Diastolic		
I H. H.		mEq./L.	mEq. (24 hr.)				
	Regular I	137–142	70–103	218	127	4 wk.	144
	Low sodium	144–136	6–10	217	132	6 wk.	135
	Low sodium + mercurial injections	134–137	360–160‡	186	115	2½ wk.	128–134
	Rice diet	136–130	1–4	180	114	5 wk.	146–137
	Rice + salt (6–12 Gm.)		141	204	118	13 days	138
II S. D.	Regular I	139–145	65–103	166	104	5 wk.	166
	Low sodium	143–137	16–19	139	95	6 wk.	160
	Low sodium + mercurial injections	136–139	266–120‡	152	100	3½ wk.	155
	Regular II	141	56	163	105	6 wk.	166
	Rice	141–139	1–4	132	86	5½ wk.	158
	Rice + 12 Gm. salt		315	151	94	2 wk.	159
III G. K.	Regular	138	90	240	136	8 wk.	130
	Low sodium	138–131	8–13	224	131	5 wk.	116
	Rice	136	7–8	236	132	4 wk.	129–115
IV R. S.	Regular I	138	80	173	106	4 wk.	131
	Low sodium	138	3–6	164	100	4 wk.	126
	Rice diet	136–132	1–3	164	99	4 wk.	118
V L. N.	Regular I	143	75	205	143	17 days	85
	Low sodium	144–132	3–9	169	125	2 months	79
	Regular II	138	97	191	136	3 wk.	83
VI G. M.	Regular diet	138	57–88	221	142	4 wk.	97
	Low sodium	133–132	12–15	230	145	6 wk.	92
VII E. W.	Regular	135	84–95	184	121	2 wk.	123
	Low sodium	136	3–9	168	110	4 wk.	116
VIII M. W.	Regular	138	68	212	122	3 wk.	133
	Rice	138	6–9	194	112	4 wk.	125

* Figures represent the range of values during each period.
† Figures denote the range of values after five days on the diet.
‡ Figures denote sodium diuresis on the first and second day of mercurial injection.

so quickly after restoration to a regular diet that it probably was caused to a large measure by fluid loss.

CASE REPORTS

CASE I. H. H., a negro man aged fifty, was a known hypertensive of twenty-five years duration. In March, 1947 he suffered a cerebral vascular accident with resultant left hemiparesis. He had complained of headaches for two years.

Upon admission to the hospital the systolic blood pressure was 230 mm. of mercury and the diastolic 135 mm. The fundi revealed Keith-Wagner changes, grade II to III. The heart was slightly enlarged to the left on x-ray examination. There was evidence of left hemiparesis. The maximum specific gravity of the urine was 1.020. He excreted 55 per cent of the phenolsulfonphthalein injected within two hours. The urea clearance was 102 per cent of normal.

The arterial blood pressures and the blood and urinary sodium values are noted in Table I. During the control period the patient's blood pressure became stabilized at a level of 218 mm. of mercury systolic and 127 mm. diastolic. In this patient the low sodium diet had no effect until ammonium chloride and two injections of mercupurin were given after six weeks of sodium restriction. A marked sodium diuresis was obtained and a persistent, significant fall in both systolic and diastolic pressures occurred. The patient was then placed on a regular diet and after the pressure had become stabilized at about the control levels he was placed on the rice diet for a period of five weeks. The fall in systolic and diastolic pressure was of about the same magnitude as occurred on the low sodium diet after mercurial injection. The decline in blood pressure was not associated with any amelioration of the headaches.

CASE II. S. D., a white man aged fifty-four, had his first cerebral vascular accident in 1943. It was at that time that his hypertension was first discovered. Since then, he has had two further cerebral vascular accidents resulting in right hemiparesis. There was no dyspnea, orthopnea or edema and only occasional headaches. Upon admission to the hospital the systolic pressure was 220 mm. of mercury and the diastolic 120 mm. The fundi showed grade II to III Keith-Wagner changes. The heart was slightly enlarged on x-ray examination. Neurologic examination showed evidence of right hemiparesis. The maximum specific gravity of the urine was 1.025 and the urea clearance was 125 per cent of normal; 50 per cent of the phenolsulfonphthalein injected was excreted within two hours.

The data on this patient are shown in Table I. During the control period the patient showed a striking fall in blood pressure. After the pressure had become stabilized at about 166/104 the patient was placed on the low sodium diet for a period of six weeks and the pressure then declined to a level of 139 mm. of mercury systolic and 95 mm. diastolic. This decline was not further augmented by the use of ammonium chloride and mercurial injections. Following the low sodium diet, the patient was placed on the regular diet again for a period of six weeks. After stabilization of the blood pressure had occurred the rice diet was instituted for a period of six weeks and there was a fall of the blood pressure to 132/85. The fall on the rice diet was slightly greater than that achieved on the low sodium diet. The addition to the rice diet of 12 Gm. of salt in enteric-coated tablets over a period of two weeks resulted in a significant rise in blood pressure.

CASE III. G. K., a white man aged fifty-eight, had a cerebral vascular accident in 1940 resulting in left hemiplegia. It was at this time that hypertension was first noted. His past history was essentially negative except for poliomyelitis at the age of eight. Upon admission to the hospital the systolic pressure was 224 mm. of mercury and the diastolic 120 mm. Examination of the fundi revealed grade III Keith-Wagner changes. There was no evidence of cardiac enlargement by x-ray. Neurologic examination revealed the presence of residual left hemiplegia and atrophy of the muscles of the right lower extremity. The maximum specific gravity of the urine was 1.019, 30 per cent of the phenolsulfonphthalein injected was excreted at the end of two hours. The urea clearance was 35 per cent of normal.

The data on this patient are shown in Table I. After a control period of eight weeks the patient was placed on the low sodium diet. The fall in systolic and diastolic pressure was slight and statistically not significant. A four-week trial on the rice diet did not alter the pressure. There was no change in the electrocardiogram, fundi or size of the heart on either diet.

CASE IV. R. S., a white man aged fifty-nine, had a cerebral vascular accident at the age of

forty-nine, with resultant right hemiparesis and motor aphasia. At that time hypertension was first discovered. The patient had no symptoms referable to hypertension prior to the occurrence of the cerebral vascular accident. Upon admission to the hospital the systolic pressure was 230 mm. of mercury and the diastolic 130 mm. There was a moderate degree of sclerosis of the peripheral vessels. There were no pulsations present in the left external carotid artery. The fundi showed mild arteriosclerotic changes. Right hemiplegia was present. The heart was not enlarged on x-ray examination. In 1940 the left common and internal carotid arteries were excised. Maximum specific gravity of the urine was 1.031; 50 per cent of the phenolsulfonphthalein injected was excreted at the end of two hours; urea clearance was 77 per cent of normal.

The data in Table I reveal a minimal fall in systolic and diastolic pressures after four weeks on the low sodium and after a similar period on the rice diet.

CASE V. L. N., a colored female aged fifty-one with tabes dorsalis for fifteen years, was admitted to this hospital in March, 1944 for custodial care. There was no history of hypertension prior to admission. Upon admission the systolic blood pressure was 180 mm. of mercury and the diastolic 120 mm. Examination of the fundi showed moderate hypertensive changes. The heart was normal in size and shape by x-ray examination. The neurologic examination confirmed the diagnosis of tabes dorsalis and there were Charcot joints in both hips. The maximum specific gravity of the urine was 1.020; 30 per cent of the phenolsulfonphthalein injected was excreted at the end of two hours; the urea clearance was 45 per cent of normal; the blood urea nitrogen was 18 mg. per cent. The urine contained no albumin; occasional white blood cells were seen upon microscopic examination. Retrograde pyelography revealed the right kidney to be rotated and the left kidney ptosed with the pelvis slightly dilated.

The patient had been hospitalized at this hospital for over three years prior to this study and all blood pressure determinations were markedly elevated. The patient was observed for seventeen days and when her blood pressure was stabilized she was placed on the low sodium diet. She was given a low sodium diet for eight weeks. A significant decline in blood pressure occurred. (Table I.) After cessation of the low sodium diet the blood pressure, which was followed for three additional weeks, began to approach the levels of the control period.

CASE VI. G. M., a white female aged thirty-two, had a history of headaches for over twenty years. Headaches were occipital and occurred in the morning upon arising. In 1943 at the age of twenty-eight she sought medical advice at which time hypertension was first discovered. In May, 1947 because of severe epistaxis the patient was admitted to another hospital where the diagnosis of malignant hypertension was made. In June, 1947 she underwent bilateral sympathectomy with diminution in frequency but not in the severity of the headaches. She was transferred to Goldwater Memorial Hospital for further care in August, 1947. Upon admission to this hospital the systolic pressure was 200 mm. of mercury and the diastolic was 140 mm. Examination of the fundi revealed grade IV Keith-Wagner changes. There was a harsh, apical, systolic murmur transmitted to the base and axilla. Fluoroscopic examination showed slight enlargement of the left ventricle. Well healed operative scars were noted in both flanks. The maximum specific gravity of the urine was 1.014; 25 per cent of the phenolsulfonphthalein injected was excreted at the end of two hours; urea clearance was 24 per cent of normal. The blood urea nitrogen was 18 mg. per cent.

The data in Table I indicate that after a period of six weeks on the low sodium diet there was no significant change in blood pressure. The patient had no relief from her headaches and there were no changes in the heart size or electrocardiogram. The patient had a progressive downhill course and died of a cerebral hemorrhage seven months after admission.

CASE VII. E. W., a colored male aged thirty-eight had complained of headaches of six months' duration which were associated with nausea but no vomiting. Hypertension was discovered two months prior to admission. Because of the increasing severity of his headaches, the patient was admitted to the hospital. His past history was non-contributory. Upon admission the systolic blood pressure was 180 mm. of mercury and the diastolic 120 mm. Examination of the fundi revealed moderately severe hypertensive changes. There was no cardiac enlargement demonstrable on physical or x-ray examination. The maximum specific gravity of the urine was 1.020; 45 per cent of the phenolsulfonphthalein injected was excreted at the end

of two hours; the urea clearance was 70 per cent of normal.

Because the patient was gainfully employed, control observations were limited to two weeks before he was placed on the low sodium diet. After a month on the restricted diet there was a statistically significant fall in systolic and diastolic pressures to 168/110. (Table I.) These changes were not of great magnitude. There was no improvement in the patient's symptoms of headache and nausea.

CASE VIII. M. W., a white widow aged forty-two, was admitted to this hospital for treatment of hypertension of five years' duration. Her only complaint was easy fatigability and malaise. There was no history of scarlet fever, nephritis or hypertension associated with pregnancy. Upon admission the systolic blood pressure was 250 mm. of mercury and the diastolic 150 mm. Examination of the fundi showed moderately severe hypertensive changes. There was no enlargement of the heart on physical or x-ray examination. The electrocardiogram was abnormal with depressed S-T segments in leads I and V_5 with diphasic T_1 and inverted TV_5; there was left deviation of the electrical axis. Maximum specific gravity of the urine was 1.028; 40 per cent of the phenolsulfonphthalein injected was excreted at the end of two hours; urea clearance was 78 per cent of normal. Blood urea nitrogen was 17 mg. per cent on admission. A retrograde pyelogram showed moderate dilatation of the right renal pelvis.

With rest in the hospital, there was a definite fall in blood pressure and after a three week control period the arterial pressure became stabilized at a lower level. The patient was placed on the rice diet for a period of four weeks and a significant decline in blood pressure occurred as noted in Table I. No change in heart size was noted. Upon discharge from the hospital after conclusion of the diet therapy the patient was somewhat improved symptomatically.

COMMENT

The low sodium diet, although monotonous, seemed to be better tolerated than the rice diet. There were no symptoms of salt deprivation in any of the patients despite the fact that some of the patients were on the diet during the hot summer months. As has been previously reported[1] there was a striking fall in blood urea nitrogen and cholesterol in the four patients on the rice diet.

A summary of our observations is charted in Table II. Of the seven patients on the low sodium diet there was no statistically signifi-

TABLE II
SUMMARY OF OBSERVATIONS

Patient	Systolic			Diastolic		
	Control	Low Sodium	Rice	Control	Low Sodium	Rice
	70 mEq. Na	13 mEq. Na	7 mEq. Na			
H. H.	218	186*	180	127	116*	114
S. D.	166	139	132	104	95	86
G. K.	240	224	236	136	131	132
R. S.	173	164	164	106	100	99
L. N.	205	169	...	143	124	
G. M.	221	230	...	142	145	
E. W.	184	168	...	121	109	
M. W.	212	...	194	122	...	112

* After six weeks of salt restriction the patient was given two injections of mercupurin.

cant fall in blood pressure in three (G. K., R. S. and G. M.). In the remaining four (H. H., S. D., L. N. and E. W.) there was a significant fall in systolic and diastolic pressures. However, in one of these (H. H.) the drop in pressure occurred only after salt deprivation for a six-week period was augmented by an injection of 1 cc. of mercupurin on two successive days. Of the five patients treated with the rice diet, three (H. H., S. D. and M. W.) experienced a significant fall in blood pressure. It is of interest that in the two patients (G. K. and R. S.) who did not respond to the rice diet there was also no drop in blood pressure while on the low sodium diet. In the two patients who experienced a fall in blood pressure on both diets (H. H. and S. D.) the fall was somewhat greater on the rice diet. In the entire series there was only one patient (S. D.) who had a fall in systolic and diastolic pressure to levels below 140/95 mm. of mercury on dietary treatment. In

this patient the systolic and diastolic pressures were only slightly elevated during the control period. Of the three patients (G. K., R. S. and G. M.) in whom there was no fall in arterial blood pressure while on salt deprivation diets, two (G. M. and G. K.) had marked impairment of renal function.

In the three patients who complained of headache there was no relief of symptoms although there was a fall in blood pressure in two of them (H. H. and E. W.). There were no significant changes in the electrocardiograms during the dietary therapy.

SUMMARY

1. Nine patients with hypertension were treated by diet. Seven received a low sodium diet adequate in protein; four received the rice diet in addition to this; one had the rice diet alone and in one patient observations were discontinued because he did not adhere to the diet.

2. Four of seven on the low sodium diet experienced a statistically significant fall in blood pressure; in three there was no change. Of five patients on the rice diet three showed statistically significant falls in both systolic and diastolic pressures but only one to a normal value.

3. The effect of the rice diet was only slightly greater than that of the low sodium diet.

4. Although there was a fall in blood pressure in five of the patients studied, there was no relief of symptoms. Although the number of patients studied is small it is believed these changes were not of sufficient magnitude to warrant the routine use of this type of therapy in the management of essential hypertension.

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Electrocardiographic Manifestations of Potassium Intoxication*

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THE electrocardiographic manifestations of potassium intoxication have been described in the literature, both in experimental animals and in man. Winkler, Hoff and Smith[1] in 1935 correlated the electrocardiographic changes with the level of the serum potassium in dogs. Chamberlain, Scudder and Zwemer[2] in 1939 and Crisman, Crisman, Calabresi and Darrow in 1943[3] made similar studies in cats poisoned with potassium salts given intravenously. Keith, King and Osterberg,[4] Keith and Osterberg,[5] Keith, Burchall and Baggenstoss,[6] Finch and Marchand,[7] Marchand and Finch,[8] Finch, Sawyer and Flynn,[9] Govan and Weiseth[10] and Martin and Wertman[11] have correlated the electrocardiographic findings with the level of serum potassium in human subjects who have developed potassium intoxication either spontaneously or following administration of potassium salts.

It has been found that there is first an increase in amplitude of the T waves as the serum potassium rises, then a decrease in amplitude of the R waves with an increase in amplitude of the S waves. As the serum potassium reaches a level of about 10 mEq./L. there is disappearance of the P waves and progressive depression of the RS-T segments with widening of the QRS complexes so that a smooth biphasic curve of the QRS-T appears. With the appearance of intraventricular block, the heart rate falls progressively until there is cardiac arrest in diastole. Other types of abnormalities have been described. Stewart and Smith[12] described changes in the T waves and RS-T segments similar to those usually attributed to myocardial damage and changes in rhythm such as incomplete heart block, complete auriculoventricular dissociation and irregularity of the ventricle simulating ventricular fibrillation, in addition to auricular standstill.

Potassium salts have been used therapeutically in the following manner: as diuretics in the treatment of heart failure, in the treatment of cardiac irregularities and of cardiovascular syphilis, as an expectorant, as an alkalinizing agent and in the electrolyte replacement therapy of infantile diarrhea. Smillie[13] in 1915 was the first to indicate the possible toxic action of potassium salts by mouth in patients with renal disease. His patient recovered. Stewart and Smith[12] emphasized this danger further since one of the patients in the cases reported by them died of cardiac arrest following use of potassium chloride as a diuretic. In none of these reports, however, were potassium levels recorded. The two patients of Finch and Marchand,[7] whose cases were reported in 1943, had both received potassium salts as a diuretic and both died of cardiac arrest; the serum potassium was elevated.

On the other hand, the earlier studies of Keith and Binger,[14] of Winkler, Hoff and Smith[15] and the more recent studies of Keith and his co-workers[4,5,16–18] leave the impression that administration of potassium is without danger even in severe renal disease unless there is oliguria or anuria with a blood urea nitrogen retention of 100 mg.

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per cent or more. The toxicity of potassium salts in patients with Addison's disease in which a spontaneous hyperkalemia and decreased renal excretion of potassium is known to occur will not be discussed further. In 1944 Ohnsty and Wolfson[19] recommended use of potassium bicarbonate as an alkalinizing agent in patients with cardiac decompensation who required sulfonamide therapy. They gave potassium bicarbonate 8.0 Gm. as the initial dose and 2.0 Gm. every two hours. They encountered no toxic effects in a series of nine cases. They were careful, however, to exclude those with severe renal disease and with Addison's disease from the patients so treated.

In recent months we have encountered two instances of auricular standstill and widespread intraventricular block associated with marked rises in serum potassium. In one, a man with cardiac failure, potassium bicarbonate was given as an adjunct to sulfonamide therapy. He showed evidence of mild renal insufficiency with a blood urea nitrogen retention of only 31 mg. per cent. In the other case, a boy of three and one-half years, the toxic effects occurred spontaneously in the course of the nephrotic stage of subacute glomerulonephritis. Data relating to these two cases form the basis of this paper.

CASE REPORTS

CASE 1.* M. S., No. 400459, an acutely ill male aged seventy-two, was admitted to the hospital December 13, 1947. He had been in excellent health until approximately eight months before admission when he had a three-day illness and was said to have had bronchopneumonia. He had a similar episode one month before admission. One week before admission he developed a cough and watery diarrhea. His temperature rose to 39.7°C. and he became confused.

Upon physical examination his temperature was 39.2°C., the pulse 104, respirations 40/min. and the blood pressure 96/56 mm. Hg. He was emaciated and coughed frequently. There was cyanosis. There was dullness at the left base anteriorly and posteriorly and fine râles were heard diffusely over both lung fields. The liver was palpable 7 cm. below the costal margin.

The blood Wassermann was negative, the hemoglobin 11.9 Gm., red blood cells 4.2 million and white blood cells 14.7 thousand. The urine showed 1 plus albumin, occasional white cells and occasional hyaline, granular and cellular casts. The blood urea nitrogen was 31 mg. per cent and the blood proteins were normal. Cultures of the blood and urine were negative. X-ray of the chest showed marked pulmonary congestion with possible small patches of bronchopneumonia widely disseminated throughout both lung fields.

He was placed in an oxygen tent, given penicillin and digitalized. He improved on this regimen. The electrocardiogram (Fig. 1A) showed changes in the T waves and RS-T segments compatible with coronary artery disease and digitalis effect. In order to evaluate the occurrence of diarrhea proctoscopy was done; no abnormalities were revealed. X-ray examination of the large bowel following a barium enema showed diverticulitis of the sigmoid colon.

On December 30, 1947, he had a recurrence of fever and was found to have dullness and coarse rhonchi at the base of the left lung with an increase in diarrhea. Sulfadiazine was given but its use was discontinued three days later because of crystalluria. In order to alkalinize the urine potassium bicarbonate 4 Gm. was given three times a day. It was thought inadvisable to give sodium bicarbonate because of the heart failure. Two days later, after a total of potassium bicarbonate 20 Gm. in a period of forty-eight hours, the pulse was 42/min. when taken on the four-hour schedule. The rhythm was totally irregular. The blood pressure was 80/48 mm. Hg and the respirations 40/min. The extremities were cold and clammy. The patient, however, offered no complaints. An electrocardiogram was taken at once. It showed auricular standstill with the pacemaker arising irregularly from a focus in the right ventricle. The QRS conduction time was 0.15 seconds. (Fig. 1B.) The serum potassium level taken at the time the electrocardiogram was taken was 10.3 mEq./L. and the serum sodium 128 mEq./L.

The potassium bicarbonate was discontinued. The next day the blood pressure was 118/60 mm. Hg and the pulse was regular with a rate of

* We are indebted to Dr. Herbert Koteen for permission to report this case.

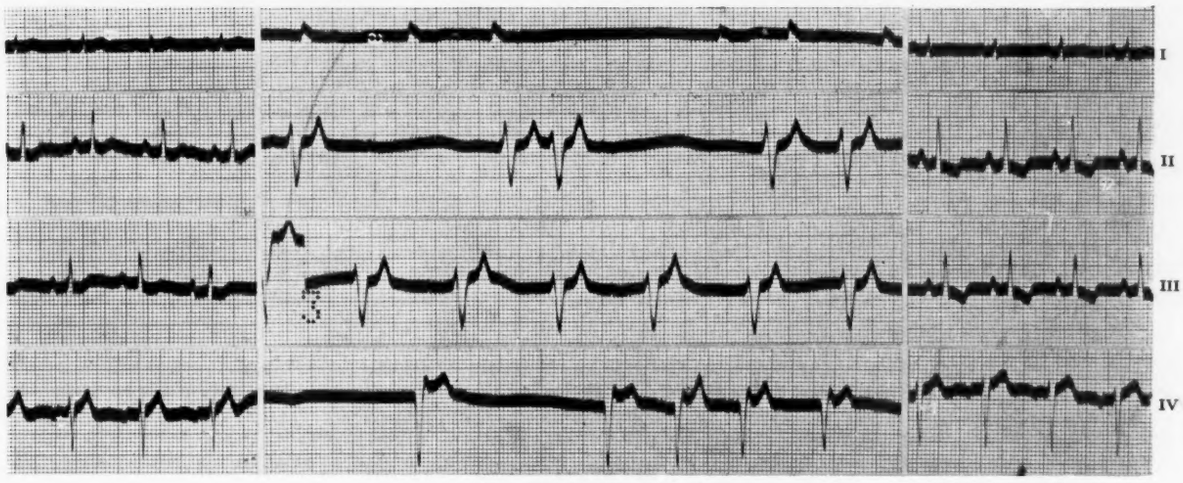

FIG. 1. In this figure are reproduced electrocardiograms of patient M. S. (Case No. 1, Hist. No. 400459), derived from the three standard leads and chest lead IV F. In this and the following figure the standardization in all leads was such that 1 millivolt produced 1 cm. deflection of the string. Divisions of the ordinates equal 10^{-4} volt. Divisions of the abscissae equal 0.04 second. In this and the following figure K = serum potassium in milliequivalents. The electrocardiograms shown in Figure 1A were taken January 2, 1948, before the administration of potassium. The electrocardiograms shown in Figure 1B were taken January 5, 1948, after the administration of potassium bicarbonate, 20 Gm. in forty-eight hours. The electrocardiograms shown in Figure 1C were taken January 6, 1948, eighteen hours after the administration of potassium had been discontinued.

90/min. He was free of complaints. The electrocardiogram now showed that marked changes had taken place in comparison with the previous record and that the form of the electrocardiogram had returned to its previous configuration. (Fig. 1C.) The serum potassium had fallen to a level of 5.9 mEq./L., normal values being considered to fall within the range of 3.9 to 5 mEq./L. The serum sodium was unchanged. The remainder of the patient's course in the hospital was uneventful and he was discharged improved on January 17, 1948.

Case II.* M. K., No. 492328, a male aged three and one-half years, was first admitted to the hospital October 29, 1947, because of swelling of the legs and he was discharged December 10, 1947. His birth and early development were normal. At the age of one and one-half years his management became difficult because of a feeding problem. At two years he was found to be anemic. He had suffered frequent respiratory infections, several of which had been treated with either penicillin or a sulfonamide. In April, 1947 his tonsils and adenoids were removed in the hope of reducing these infections. He had had no known contagious disease. Two days before admission he awoke with swollen eyelids and on the morning of admission his legs were swollen. He had had frequency of urination, with nocturia four to five times a night for several days.

Upon physical examination the significant findings were as follows: the blood pressure was 108/60 mm. Hg. The pulse rate was 110/min. and there was moderate edema of the eyelids and feet. The results of serologic tests were negative and the blood count was within normal limits. The urine specific gravity ranged from 1.010 to 1.030. The albumin in the urine ranged from 3 to 4 plus; there were a few red cells and white cells, and hyaline and granular casts upon microscopic examination. The blood urea nitrogen varied from 10 to 57 mg. per cent; the CO_2 combining power was 56.3 vol. per cent; the serum chlorides (as NaCl) were 105 mEq./L. The serum albumin was 2.0 Gm. per cent and serum globulin 2.4 Gm. per cent. The sodium was 141 mEq./L. The sedimentation rate was 16.5 mm. in one hour. The renal function tests showed a phenolsulphonphthalein excretion of 30 per cent in five hours and a urea clearance of 19.3 per cent. Blood cultures were negative, and nose and throat cultures grew no hemolytic

* We wish to thank Dr. S. Z. Levine and Dr. H. Barnett for permission to report these data of this patient.

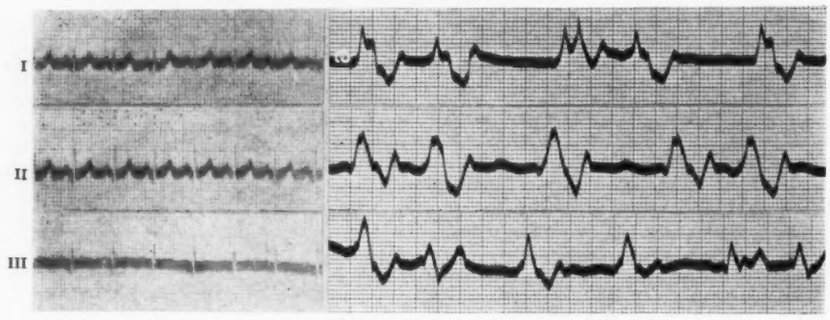

FIG. 2. In this figure are reproduced electrocardiograms of patient M. K. (Case No. 2, Hist. No. 492328) derived from the three standard leads. The electrocardiograms shown in Figure 2A were taken December 1, 1947, during the first admission to the hospital before the development of potassium intoxication. The electrocardiograms shown in Figure 2B were taken January 10, 1948, during the second admission to the hospital showing evidence of potassium intoxication.

streptococci. The electrocardiogram was normal. (Fig. 2A.)

While in the hospital, he developed an upper respiratory infection upon two occasions, during each of which the edema increased. He was treated with penicillin in addition to the basic regimen of a high-protein, low-salt diet, and on each occasion as the infection subsided he had a good diuresis. He was discharged after six weeks in the hospital with a diagnosis of subacute glomerulonephritis with nephrosis.

He was re-admitted to the hospital on January 10, 1948, having contracted a respiratory infection several days before. In association with this he had gained weight. The blood pressure was 90 mm. Hg systolic level, but the diastolic could not be obtained; the pulse rate was 114/min. He appeared acutely ill. The respirations were 24/min. There was moderate ascites and anasarca. The urine contained 4 plus albumin, 1 to 2 white cells per high power field and many granular casts. The white blood cell count was 35.1 thousand, the blood urea nitrogen was 44.5 mg. per cent, calcium 11.3 mg. per cent, phosphorus 8.6 mg. per cent, serum chlorides (as NaCl) 93.5 mEq. L., sodium 120.1 mEq., potassium 10.6 mEq./L. and proteins 3.8 Gm. per cent.

He was placed in an oxygen tent. Shortly after admission the pulse was found to be 68/min. Auscultation of the heart revealed a slow irregular rhythm, each beat being associated with three distinct sounds suggesting a gallop rhythm. An electrocardiogram showed auricular standstill with the pacemaker arising irregularly from a focus in the right ventricle giving rise to coupled rhythm in all leads. (Fig. 2B.) The rate was 70/min. The QRS time varied between 0.20 and 0.26 seconds. He was given salt and salty broth by mouth with temporary improvement. The rhythm became regular, and he was allowed out of the oxygen tent. The next day he became restless, the pulse could not be obtained and he expired. Postmortem examination revealed no pathologic changes in the heart and the kidneys showed minimal evidence of renal disease.

COMMENT

The importance of the rôle of potassium in cardiac physiology has been well substantiated by experimental and clinical data. Except for the studies of Stewart and Smith[12] and of Thomson[20] in the past decade and the recent report of Tarail,[21] it has been the consensus that potassium intoxication can assume dangerous proportions only in the presence of severe renal disease. The two cases presented herein indicate that this is not always the case.

The first patient had only slight nitrogen retention and no oliguria, but with doses of potassium which were not large, namely, 4 Gm. of the bicarbonate three times a day for two days to a total dose of 20 Gm., he developed potassium intoxication. He was given no therapy to counteract the potassium effects because it was thought that since he had no evidence of severe renal disease and was without evidence of cardiac

failure at this time the kidneys would excrete the excess potassium if the salt was discontinued. This proved to be the case as with excretion of the drug normal cardiac mechanism was restored.

At this point it is of interest to note that of the cases reported by Stewart and Smith[12] in 1941 Case v, on a dose of potassium chloride of 8 Gm. a day and with a blood urea nitrogen retention of only 60 mg. per cent, developed fatal potassium intoxication as shown by auricular standstill and intraventricular block in the electrocardiogram, with death due to cardiac arrest. The level of blood potassium was not estimated in this patient.

The second patient had subacute glomerulonephritis in a nephrotic stage, with oliguria. He had been on a low-salt diet for many months, such that at the time of his last admission his serum chlorides were 93.3 mEq./L. and his sodium was 120 mEq./L. The potassium was 10.6 mEq./L. at the time that the electrocardiogram showed auricular standstill and intraventricular block. He was treated with salt by mouth with temporary return of regular rhythm but, in the absence of further electrocardiograms and further electrolyte studies, the exact mechanism of his subsequent exitus is not certain. It seems likely that he died of potassium intoxication, particularly as the autopsy findings gave no clue as to the cause of death. A review of the literature reveals that this represents the first reported case of death from potassium intoxication in the nephrotic stage of subacute glomerulonephritis with only moderate nitrogen retention.

The electrocardiographic manifestations of potassium intoxication in these two cases are unmistakable, and it was the electrocardiogram in each case which pointed the way to the correct diagnosis. Auricular standstill is a rare occurrence, which has been pointed out by Rosenbaum and Levine,[22] and has usually been attributed to the toxic effect of either digitalis or quinidine. It is difficult to be certain of the diagnosis of auricular standstill when the ventricular complexes assume a regular and supraventricular form as a nodal rhythm with P waves buried in the QRS complexes may have the identical pattern. However, when no P waves are seen in the electrocardiogram and there is intraventricular block with an irregular rhythm it is apparent that auricular standstill is present. Thus, potassium intoxication should be considered as a possible cause in addition to the other known causes such as digitalis and quinidine intoxication. If potassium is implicated in the presence of these two electrocardiographic abnormalities, it is likely that the serum potassium level will be about 10 mEq./L. Indeed, in both of these cases the electrocardiographic diagnosis of potassium intoxication was made and this was the basis for the potassium analyses.

Experience with the treatment of this condition has been limited as the number of cases is small. The natural history of the phenomenon is such that either sudden death from cardiac arrest will occur in a few hours or recovery will ensue, the outcome depending upon the nature of the underlying renal defect. The problem, therefore, is to recognize the condition promptly and to prevent cardiac arrest by prompt and appropriate treatment. Potassium salts should, of course, be discontinued if these are being given, and this may be sufficient.

In the treatment of auricular standstill with ventricular rhythm calcium ions have been used by Stewart and Smith,[12] by Finch, Sawyer and Flynn[9] and by Govan and Darrow[10,23] because of their known property of increasing the irritability of cardiac muscle. In the case reported by Stewart and Smith[12] calcium gave a transient increase in cardiac rate but was ineffective in preventing eventual cardiac arrest.

After observing the transient effect of calcium ions Finch, Sawyer and Flynn[9] were able to correct temporarily the potassium intoxication of patients in the terminal stages of renal disease by use of 3 per cent sodium chloride intravenously. The effect was prompt and dramatic. In one case they

injected 410 cc. of salt solution in thirty-five minutes with return of regular rhythm five minutes later.

In studies relating to the rôle of potassium in the body economy it has been shown that the deposition of glycogen is accompanied by a transfer of potassium from the extracellular phase to the intracellular phase. This was reported by Fenn[24] in rats and by Martin and Wertman[25] in patients with diabetic acidosis treated with insulin. Moreover, Gass, Cherkasky and Savitsky[26] induced attacks of paralysis in patients with familial periodic palsy by administering glucose intravenously. It is recalled that attacks of paralysis in this disease are accompanied by a low level of potassium in the blood. This effect of glucose was turned to advantage by Govan and Darrow[23] who successfully treated potassium intoxication in an infant with diarrhea by use of hypertonic glucose intravenously to promote glycogen deposition; reduction of the level of serum potassium resulted from this measure. They used calcium gluconate simultaneously but, in view of the experience just cited, it seems unlikely that it was of major importance in the therapeutic effect which followed. Their patient had a serum potassium of 12.3 mEq./L., this is probably the highest level reported in man with recovery.

It is paradoxical that the heart failure which may arise secondary to potassium intoxication should be treated by means of intravenous glucose and saline. These measures may, however, be life-saving. In the light of these considerations it is interesting to review the data of Case II, in which postmortem study revealed evidence of only minimal renal disease. More vigorous therapy in the form of intravenous glucose and saline might have overcome the potassium intoxication in this patient, thereby controlling what might have been a transient episode in an otherwise chronic illness.

The danger of potassium administration, even in the presence of mild renal disease, is emphasized. It is apparent that potassium salts administered for any reason should be used with extreme caution if there is any possibility of underlying renal disease. This is particularly pertinent in view of the current use of the new salt substitutes containing potassium which have been advocated for cardiac patients. Some of these preparations contain 35 per cent potassium[27] with instructions that they may be used in the same quantity as ordinary table salt and without warning as to possible toxic effects. Use of 5 to 10 Gm. of these salt substitutes per day would entail the ingestion of 2 to 4 Gm. of potassium a day. This, even with mild renal disease, may be sufficient to cause potassium intoxication.

SUMMARY

Two cases of potassium intoxication have been presented in which auricular standstill and widespread intraventricular block appeared in the electrocardiograms at a time when the serum potassium had risen to a level of 10 mEq./L. or higher. One occurred following administration of therapeutic amounts of potassium bicarbonate in the presence of only slight urea nitrogen retention. The other occurred spontaneously in the course of the nephrotic stage of subacute glomerulonephritis.

It appears that physiologic saline solution and hypertonic glucose should promptly be administered intravenously in treatment of the cardiac manifestations of potassium intoxication.

The electrocardiographic manifestations of potassium intoxication are reviewed and the danger of administering potassium salts, even in the presence of only mild renal disease, is emphasized.

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Relation of Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances*

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ELECTROCARDIOGRAPHIC disturbances have been related directly to abnormalities in the concentration of serum potassium.[1–10] Abnormal reduction in the concentration of serum potassium has been associated with depression of the S-T segment and the T wave, and with increase in the P-R and Q-T intervals. These abnormalities have been said to disappear as the concentration of serum potassium increases.[4–8] Abnormal elevation of the concentration of serum potassium has been associated with peaked T waves, prolonged intraventricular and atrioventricular conduction, disappearance of the P wave and depression and obliteration of the S-T segment.[1–3,9,10]

The purpose of this study is to determine in man the relationship between abnormalities in the concentration of serum potassium and electrocardiographic findings. This analysis is based on a survey of the concentrations of serum potassium and of concomitant electrocardiograms in patients suspected of abnormalities in the metabolism and excretion of potassium. One group of patients had low concentrations of serum potassium and cellular depletion of the ion. Another had elevated concentrations as the result of inadequate excretion of the ion. Detailed chemical and metabolic data pertaining to these patients are reported elsewhere.[11,12]

EXPERIMENTAL PROCEDURE AND METHODS

Electrocardiograms and specimens of blood for chemical analysis were taken from nineteen patients who had normal renal function and possible deficits of potassium. Low concentrations of serum potassium were observed in four of the patients before treatment with potassium. Significant quantities were retained in the cellular phase when potassium was administered.[11] The chemical and electrocardiographic findings in these four patients will be presented. All four were sustained almost entirely on parenteral fluids and were losing abnormal quantities of gastrointestinal fluid.

Seventy electrocardiograms and simultaneous chemical studies were carried out in nineteen cases of renal insufficiency. These patients were part of a group of fifty-one consecutive patients in whom the concentration of blood non-protein nitrogen was found to be greater than 100 mg. per cent. The metabolism and excretion of potassium in these patients will be discussed elsewhere.[12]

Electrocardiograms were usually taken with a conventional amplifier type instrument with photographic recording; occasionally a direct writing instrument was used.† All tracings were taken and mounted by the same observer and were standardized to a deflection of 1 cm. per millivolt.

The chemical methods have been reported previously from this laboratory;[11,12] diagnoses and certain clinical details are appended to the illustrations and to Table I.

† "Visocardiette," Sanborn Company.

* From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn. This work was done during the tenure of a Life Insurance Medical Research Fellowship.

TABLE I

RESULTS OF SIMULTANEOUS CHEMICAL AND ELECTROCARDIOGRAPHIC STUDIES IN NINETEEN PATIENTS WITH RENAL INSUFFICIENCY

Patient	Diagnosis	Outcome	Preceding 24-hour Urine Vol. (cc.)	Highest Serum K (mEq./L.)	Time before Death (Hr.)	Elevated K Effect (E.C.G.)	Blood NPN (mg. %)	Serum						Hypertension	Pericarditis	Digitalis	Coronary Disease	Anemia
								CO_2 (mEq./L.)	Cl (mEq./L.)	Na (mEq./L.)	Ca (mg. %)	P (mg. %)	Prot. (Gm. %)					
R. S.*	Carcinomatous ureteral obstruction	D	0	8.1	3	+	245	....	91.2	127.0	...	....	....	0	0	0	0	+
P. DeB.*	Acute glomerulonephritis	D	0	8.1	0	+	151	13.1	85.8	128.3	9.6	....	....	+	0	+	0	+
P. M.*	Lower nephron nephrosis	D	110	8.3	6	+	201	....	86.2	121.9	6.2	8.7	5.21	+	0	0	+	0
L. T.*	Pyelonephritis	D	95	6.9†	12	0	185	11.0	....	136.3	...	....	....	0	0	+	0	++
J. P.	Nephrosclerosis	D	0	7.5	15	+	255	....	91.9	.....	...	....	....	+	0	+	0	++
F. S.	Nephrosclerosis	D	inc.	4.3	>24	0	88	24.3	93.4	131.0	...	....	....	+	0	+	0	++
C. K.	Intercap. glomerulosclerosis	D	740	5.8	<24	0	204	14.2	93.7	134.9	5.2	13.6	4.90	+	0	+	0	+
A. M.	Nephrosclerosis	D	100	5.7	20	0	245	10.5	94.1	131.4	...	....	....	+	0	0	0	++
W. S.*	Nephrosclerosis	D	986	6.0	<24	0	311	....	....	.....	...	....	....	+	+	+	+	++
W. M.	Lower nephron nephrosis	R	210	6.4	....	0	172	17.3	84.3	133.0	9.2	7.1	6.30	+	0	+	0	+
A. G.*	Polycystic kidneys	D	inc.	6.2	13	0	205	....	....	116.3	...	....	....	+	0	+	0	+
O. T.*	Nephrosclerosis	D	300	4.0	>24	0	119	16.9	102.2	137.9	...	....	....	+	0	+	0	++
A. M.*	Pyelonephritis	D	1500	5.0	>24	0	250	....	....	.....	7.1	11.1	4.70	+	0	+	+	+++
S. M.	Pyelonephritis	R	3500	5.5		0	144	....	....	137.9	8.4			+	0	+	0	++
P. R.	Chronic glomerulonephritis	D	1000	6.1	>24	0	120	22.8	91.2	137.8	7.6	8.5	5.60	+	+	+	0	+
P. A.	Nephrosclerosis	D	120	4.0	16	0	100	18.7	109.1	.....	...	....	....	+	0	0	0	0
J. G.*	Disseminated lupus erythematosus	D	inc.	5.5	>24	0	125	24.1	101.0	141.3	...	....	....	+	+	+	0	+
A. C.	Nephrosclerosis	D	inc.	6.3	>24	0	321	8.9	84.6	130.0	5.0	16.8	5.60	+	+	+	0	++
G. B.	Nephrosclerosis	D	1050	6.6	>24	0	133	19.1	77.5	122.3	...	....	....	+	0	+	+	++

The groups in which cardiotoxic effects of potassium were and were not found were comparable except for marked elevations in concentration of serum potassium in the former. inc. = incontinent; + = present; 0 = absent; D = died; R = recovered.

* Autopsy.

† Serum potassium at death was 8.7 mEq./L.

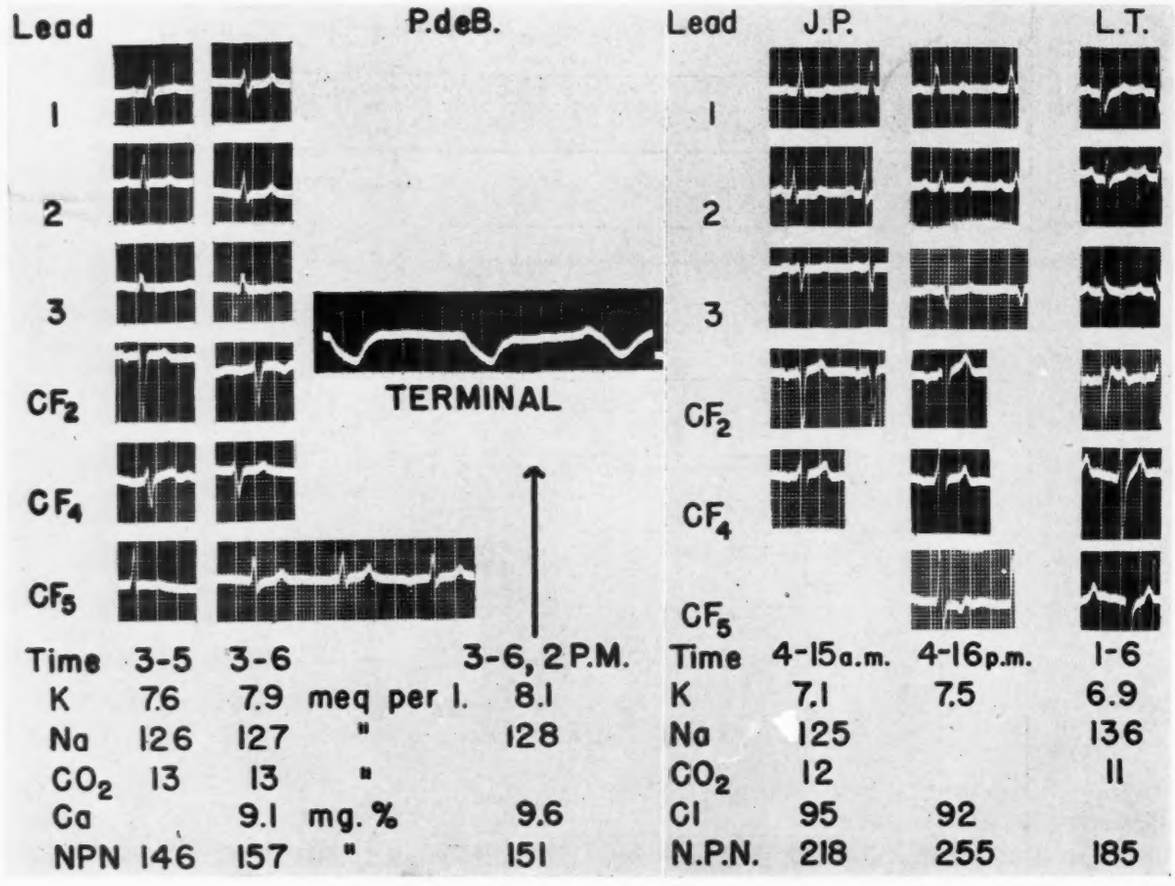

FIG. 1. Potassium effect consisting of absent P waves, increase in duration of QRS and peaked T waves was first evident on the morning of 3-6. At death cardiac arrest preceded respiratory arrest. Three ventricular complexes were registered in lead I just prior to death. In this and in subsequent figures the concentrations of serum calcium and of blood non-protein nitrogen are given in mg. per cent. Other concentrations are expressed in mEq./L.

FIG. 2. Possible effect of potassium in J. B. became evident on 4-16, ten hours before death. Increase in P-R interval, slight increase in duration of QRS and peaked T waves occurred. The tracing of L. T. is that taken twelve hours before death; there is no definite evidence of the toxic effect of potassium. The serum potassium at death was 8.7 mEq./L.

Results. The data are presented in Tables I and II and in Figures 1 to 8.* The entire group of nineteen cases of renal insufficiency was analyzed with respect to features which may produce electrocardiographic abnormalities. (Table I.) Electrocardiographic disturbances consistent with the effects of a high concentration of serum potassium were observed in four of the nineteen cases. These four differed from the other fifteen apparently only with respect to the presence of marked elevation of serum potassium in the former group.

The principal electrocardiographic abnormalities referable to elevation of concentration of potassium were peaked T waves and increase in the duration of the QRS complex. (Figs. 1 to 4.) The peaked T waves were not always abnormally large in amplitude. They were usually upright in the limb leads but occasionally were negative in the CF leads. Depression or occasional elevation of the S-T segment was sometimes noted in patients not receiving digitalis. (Figs. 3 and 4.) Increase in the P-R interval and, in one instance, actual disappearance of the P wave (Fig. 1) occurred as the concentration of serum potassium rose. Changes in the ratio of the deflections of R/S were minimal. These findings were similar to those described previously in cases of potassium intoxication.[3,9,10,13]

* The concentrations of serum calcium and of blood non-protein nitrogen are expressed in milligrams per cent. Other concentrations are expressed in mEq./L.

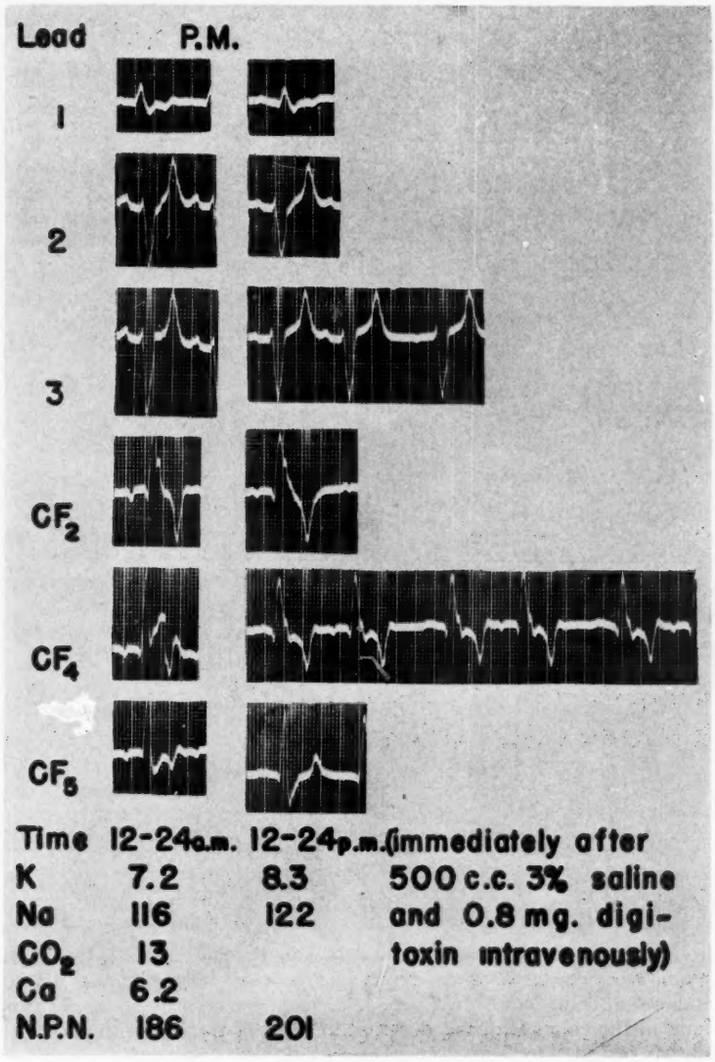

FIG. 3. Striking electrocardiographic evidence of the cardiotoxic effects of potassium; tracings taken eighteen and six hours before death. No digitalis compound had been given prior to 12-24 P.M. The appearance of the electrocardiogram was not improved by administration of saline and 0.8 mg. of digitoxin.

Electrocardiographic findings in relation to concentrations of serum potassium are presented in Table II and are taken from the data of Figures 1 to 4. The electrocardiographic effect of a given elevated concentration of serum potassium was variable. There were advanced electrocardiographic disturbances at a concentration of 7.2 mEq./L. as seen in one case. (Fig. 3.) No effect was apparent at 7.6 mEq./L. in another. (Fig. 1.) The action of potassium was observed at 6.8 mEq./L. in R. S. (Fig. 4) but could not be demonstrated at 6.9 mEq./L. in L. T. (Fig. 2.) The intensity of effect on the electrocardiogram in the group as a whole was not directly proportional to the concentration of potassium in serum. Increasing electrocardiographic effect *in a given patient*, however, was associated with increases in concentration of potassium. (Table II, Figs. 1 to 4.)

No toxic action of potassium was found at concentrations of serum potassium below 6.8 mEq./L. Cardiotoxic findings were sometimes present between 6.8 and 7.6 mEq./L. Cardiotoxic action was found regularly at concentrations greater than 7.8 mEq./L.

The electrocardiographic abnormalities referable to potassium were striking, and occurred at lower concentrations of serum potassium in

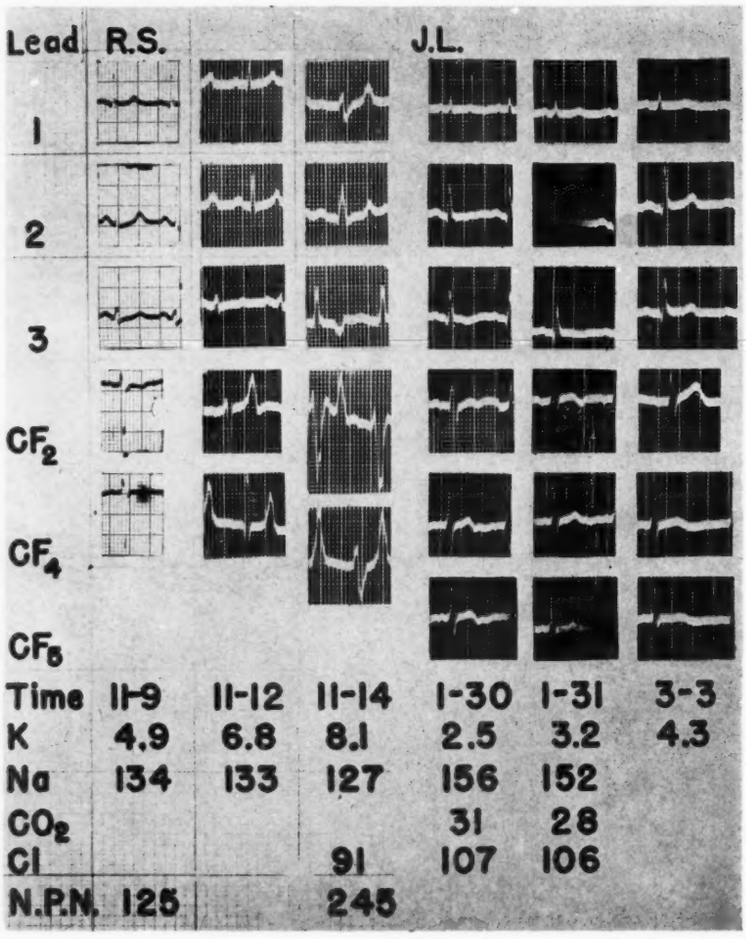

FIG. 4. In R. S. potassium effect was definitely present on 11-12. By 11-14, two hours before death, these effects had become more pronounced; no digitalis compound had been given. J. L. had been operated upon for carcinoma of the colon and had developed deficit of potassium in the postoperative period. On 1-31 despite an increase in concentration of serum potassium there was no appreciable change in the E.C.G. By 3-3, coincident with an increase in serum potassium, T waves in most of the leads had increased in amplitude. No digitalis compound had been given.

the two patients who were not digitalized. (Figs. 3 and 4.) One of the digitalized patients was followed for one week prior to death. (Fig. 1.) The serum potassium rose from 6.4 to 8.1 mEq./L. at death. Potassium effect appeared at 7.9 mEq./L. Three grossly disorganized, extremely prolonged ventricular complexes were recorded just before death. Cardiac arrest preceded respiratory arrest. In this patient slight increases in serum potassium were associated with striking changes in the electrocardiogram.

The data do not permit generalizations with respect to the effects of alterations in pH, serum calcium or sodium on the intensity of the potassium effect. In one instance infusion of hypertonic saline did not ameliorate the electrocardiographic abnormalities. (Fig. 3.) The toxic effect of potassium was found only in oliguric patients but there were some oliguric patients in whom abnormally high concentrations of serum potassium were not observed. (Table 1.)

The principal electrocardiographic findings referable to low concentration of serum potassium were low amplitude of the T waves and prolongation of the Q-T interval. (Figs. 4 to 8.) These findings were present in a case of renal insufficiency with abnormal depression of the serum potassium. (Fig. 5.) There was no consistent relationship between changes in serum potassium and changes in the electrocardiogram. Since concentrations of serum calcium

were not determined, no conclusions can be drawn with respect to changes in electrical systole. Digitoxin was given after the tracing of March 21st.

The four patients with low concentrations of serum potassium and normal renal function had been sustained on parenteral fluids containing no potassium. Deficit of potassium was produced by losses of the ion in the urine and in gastrointestinal fluids. Concentrations of serum potassium were increased by the slow intravenous administration of potassium salts. One of the patients (M. M., Fig. 6) was suspected of having heart disease (coronary arteriosclerosis) and was digitalized. There was no clinical evidence of heart disease in the others.

TABLE II
RELATIONSHIP OF ELEVATED CONCENTRATION OF SERUM POTASSIUM TO EFFECT ON THE ELECTROCARDIOGRAM

Serum Potassium mEq./L.	Patient	E.C.G. Evidence of Effect of Potassium		
		None	Moderate	Pronounced
6.8	R. S.	..	+	
6.9	L. T.	+		
7.1	J. P.	+		
7.2	P. M.	..	..	+
7.5	J. P.	..	+	
7.6	P. DeB.	+		
7.9	P. DeB.	..	..	+
8.1	P. DeB.	..	..	+
8.1	R. S.	..	..	+
8.3	P. M.	..	..	+

At concentrations of serum potassium below 7.9 mEq./L. at least, E.C.G. findings cannot be accurately predicted simply from knowledge of these concentrations.

The T waves were low in all of the patients initially; these waves increased in amplitude as the serum potassium rose in two of the patients. The increase in serum potassium was moderately and markedly correlated, respectively, with increased height of the T wave in J. L. (Fig. 4) and A. M. (Fig. 7.) The T wave changes were not clearly related to increase in concentration of serum potassium in the other two cases. (Figs. 6 and 8.)

Prolongation of the Q-T interval occurred in three of the four patients when the concentration of serum potassium was low. (Figs. 6 to 8.) Disappearance or persistence of this abnormality was not definitely related to a rise in concentration of serum potassium to within the normal range. Disturbances in the P-R interval and in the height of the S-T segment were not striking features of the electrocardiograms.

COMMENTS

The electrocardiographic findings of potassium intoxication were present only when the concentration of serum potassium was elevated. High concentrations of serum potassium with associated cardiac disturbances reflected in electrocardiographic abnormalities may have been factors contributing to the death of four of nineteen patients with severe renal insufficiency. This incidence is inconsistent with the view that potassium intoxication is an extremely rare event in patients dying of renal insufficiency.[14] It supports the hypothesis, which was based on electrocardiographic evidence alone, that the cardiotoxic action of potassium occurs more frequently than is ordinarily suspected in patients dying of renal insufficiency.[15]

There were numerous measurements of concentrations of serum potassium between 6.0 and 7.0 mEq./L. in this study. Since in one patient peaked T waves were noted between 6.5 and 7.0 mEq./L., this range is an approximation of the lowest concentrations at which cardiotoxic results of potassium could be demonstrated. The lowest corresponding concentration of serum potassium found under different circumstances in the dog was 5.0 mEq./L.[1,2] Peaked T waves were the first sign of elevation of serum potassium both in this study and in the dog.[1,2] Subsequent disturbances in the QRS interval, P-R interval, S-T segment and P waves were found to occur concurrently in the present study.

Although in a given patient increase in the severity of electrocardiographic disturbance was associated with abnormal elevation in the concentration of serum potassium, the appearance of the electrocardiogram at elevated concentrations of serum potassium differed widely from case

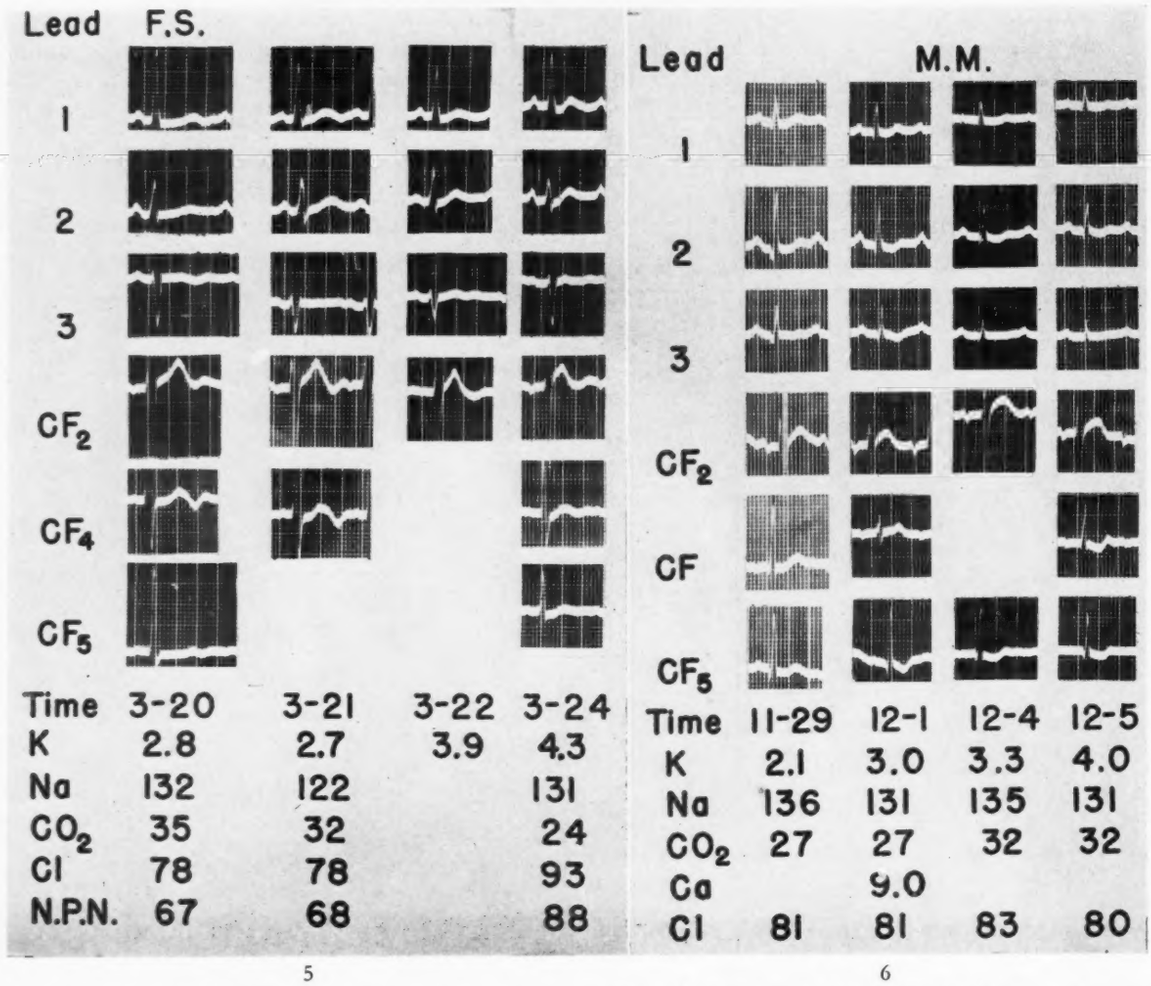

FIG. 5. Case of renal insufficiency with low serum potassium. There is no demonstrable relationship between changes in the concentration of serum potassium and changes in the E.C.G. Digitoxin was given after the tracing of 3-21.
FIG. 6. The patient had cirrhosis of the liver. Intake had been low in potassium for several weeks. There is no demonstrable relationship between changes in the concentration of serum potassium and changes in the electrocardiogram; digitoxin had been given.

to case. Comparable differences were disclosed to a certain extent in fundamental studies of the cardiotoxic action of potassium in the dog.[1,2] Therefore, an evaluation of the relation between hyperkaliemia and actual cardiac damage apart from that estimated from the electrocardiogram is appropriate. There may be considerable discrepancy between the degree of cardiac disease as evaluated by clinical and pathologic criteria and the degree of electrocardiographic disturbance.[16] Hoff, Winkler and Smith have shown that during stimulation of the vagus of the dog comparatively slight elevations of the concentration of serum potassium may result in temporary cardiac arrest without advanced electrocardiographic disturbances consistent with potassium effect.[17] Under certain circumstances the cardiac damage related to elevated extracellular concentration of potassium may exceed the degree of observed electrocardiographic disturbance. This may apply particularly to patients with renal insufficiency since numerous factors may reinforce or mask abnormalities in the electrocardiogram. Conversely, it is possible that the degree of cardiac disturbance related to the effect of potassium may appear spuriously great if judged solely

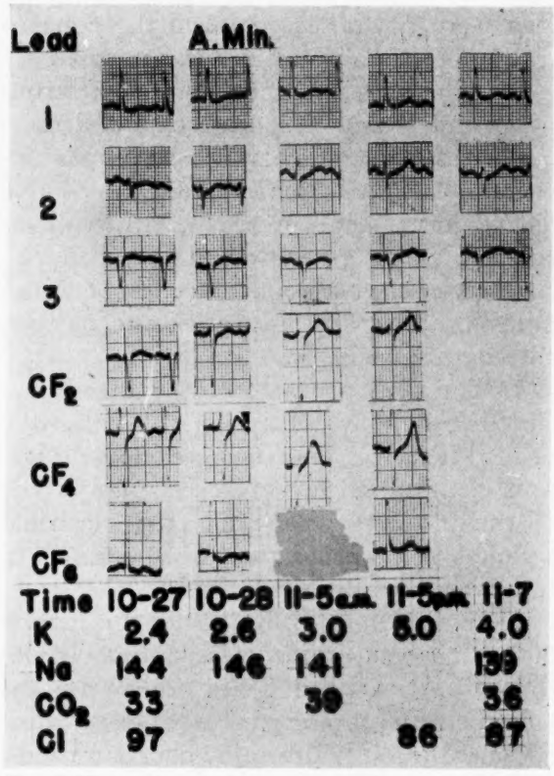

FIG. 7. The patient had been operated on for carcinoma of the common bile duct. There is a direct relation between the height of the T wave and the concentration of serum potassium. Patient had received 6 Gm. of potassium by slow intravenous infusion just prior to the second tracing of 11-5.

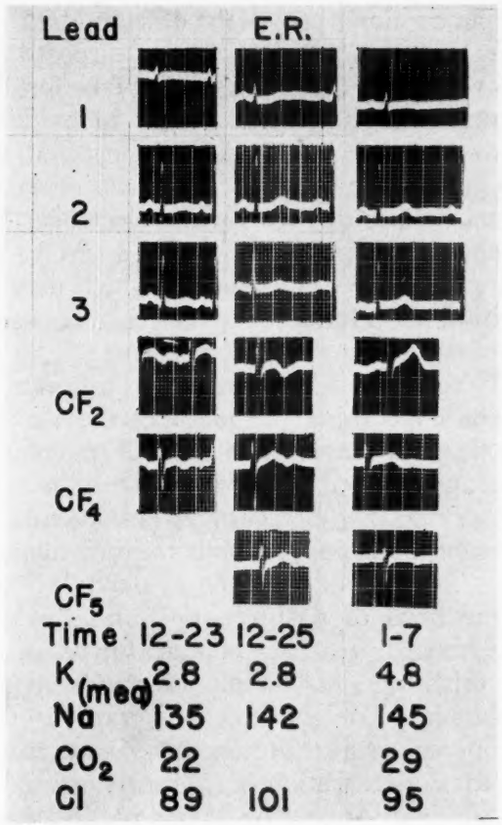

FIG. 8. The patient had intractable vomiting of unknown etiology. There is no definite relation between changes in the concentration of serum potassium and the changes in the electrocardiogram.

by the intensity of the electrocardiographic findings.

The electrocardiographic findings in the present group of cases of low concentration of serum potassium are similar to those described by others.[4–8] Changes in these findings were poorly correlated with changes in concentration of serum potassium in three of the five cases. What are possible explanations of this discrepancy? Electrocardiographic disturbances indistinguishable from those of hypokaliemia may occur in other states affecting the heart.[16] Digitoxin was being given to two of the patients and may have prevented elevation of the T wave when the serum potassium became normal. Aside from other possible sources of damage to the heart it may be that some form of more permanent cardiac damage, which persists after the hypokaliemia has been corrected, occurs during deficiency of potassium. Focal cardiac lesions have been produced in animals by deficits of potassium.[18]

The possible value of parenteral therapy with potassium to patients with normal kidneys and cellular deficit of the ion has been emphasized.[11,15–21] Certain of these patients often in association with dehydration, sodium depletion and peripheral vascular collapse have been found to have elevated concentrations of serum potassium. Based on experiments in dogs,[1,2] it has been assumed that serious cardiotoxic action of potassium does not occur in man until the concentration of serum potassium reaches 10 to 12 mEq./L.[19,22] Definite electrocardiographic disturbances related to the effect of extracellular potassium occurred in renal insufficiency in man at serum concentrations of 6.8 to 7.9 mEq./L. in the present study. Neither the present line of

evidence nor that derived from data on the dog can be logically transposed to provide conclusive limits of safety for the administration of potassium to patients without severe renal insufficiency. But the range of dangerous concentrations of serum potassium as defined by the electrocardiographic abnormalities in this group of patients provides an analogy which may be helpful in minimizing the risk of using potassium as a therapeutic agent.

Certain tentative generalizations can be made concerning the place of the electrocardiogram in the control of potassium therapy. When electrocardiographic evidence of the effect of hyperkaliemia is present, potassium administration is dangerous. The absence of such evidence at concentrations of serum potassium at which electrocardiographic changes may occur in other patients does not exclude hyperkaliemia. The electrocardiogram is not properly a substitute for the measurement of the concentration of serum potassium.

Suddenly appearing flaccid paralyses and other symptoms and signs attributed to both low and high concentrations of serum potassium have been observed in patients not having familial periodic paralysis.[3,7,8,21,23] These findings were absent in reports of other similar patients and in the present series.[6,9,10,21,24] Some unknown factors as well as the concentration of serum potassium may play a rôle in the production of the paralysis.

SUMMARY

1. Electrocardiograms and blood samples for simultaneous chemical analyses were taken from nineteen patients with severe renal insufficiency. Similar studies were made in five patients with diminished and, subsequently, normal concentrations of serum potassium.

2. Electrocardiographic findings referable to the toxic effect of potassium were observed in four of the patients with renal insufficiency when the concentration of serum potassium was elevated. These findings were not observed when the concentration of serum potassium was normal.

3. The range of concentration of serum potassium within which associated electrocardiographic disturbances sometimes occurred was 6.8 to 7.6 mEq./L. These disturbances were present consistently at concentrations greater than 7.8 mEq./L. At a given elevated concentration of serum potassium the appearance of the electrocardiogram varied widely.

4. The most characteristic changes associated with hyperkaliemia in this series were peaked T waves and increase in the duration of the QRS complex. Low amplitude of the T wave and prolonged electrical systole were the most frequent findings in the group with hypokaliemia.

5. In three of the five patients elevation of the concentrations of serum potassium to normal values did not ameliorate the electrocardiographic disturbances which presumably resulted from low concentrations.

6. Implications of the present study for the problem of the use of potassium in treatment have been discussed.

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Influence of the Serum Potassium and Other Electrolytes on the Electrocardiogram in Diabetic Acidosis*

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RECENT investigations have related the changes in the electrocardiogram of patients with diabetic acidosis to alterations in certain electrolytes. In early studies Hepburn and Graham,[1] Taterka[2] and Smith and Hickling[3] described certain changes in the electrocardiogram but did not believe they could be attributed to acidosis. In 1934 Klingenberg[4] studied ten patients with this type of metabolic disturbance and found the electrocardiogram to be normal in only one subject. In 1937 Bellet and Dyer[5] described changes in the electrocardiogram in patients with diabetic acidosis that were both consistent and reversible. The chief alterations observed by these workers were lengthening in the Q-T interval, depression of the S-T segments and inversion of the T waves. Of particular interest was their observation that these alterations occurred approximately twenty-four hours after insulin therapy had been instituted, at a time when the acidotic state had been relieved by appropriate therapy. Martin and Wertman[6] found that 43 per cent of their patients with diabetic acidosis who had prolongation of the Q-T intervals showed a low serum potassium or calcium (total or ionized). Their report also emphasized the high degree of correlation between low T waves and low serum potassium levels.

The present report is based on a study of the relationship to and the effect of changes in the serum potassium and other electrolytes on the electrocardiogram in forty-five patients during and upon emergence from diabetic acidosis.

METHOD AND MATERIALS

The diagnosis of diabetic acidosis was established in each of forty-five patients by the usual clinical criteria; these included a carbon dioxide combining power of less than 14 mEq. and a blood sugar greater than 200 mg. per cent.

Upon admission to the hospital venous blood was taken for determination of the blood sugar,[7] carbon dioxide combining power,[8] pH, protein,[9] chloride,[10] blood urea nitrogen,[11] calcium,[12] sodium[13] and potassium.[13] Simultaneously an electrocardiogram including leads I, II, III and precordial leads CR_2, CR_3, CR_4 and CR_5 was taken. These studies were repeated at intervals varying from one to twelve hours after the first administration of insulin until the clinical condition, the chemical and the electrocardiographic findings had returned to normal.

These patients all received the same type of therapy, the amount of therapeutic agent being varied according to the severity of the acidosis and the state of cardiovascular embarrassment. All received regular insulin subcutaneously, in divided doses, the total amount varying from 150 to 800 units. All were given at least 2,000 cc. of isotonic sodium chloride by clysis; none received more than 3,000 cc. in the first twelve hours. The total amount of fluid administered during the first twenty-four hours did not exceed 6,000 cc. although most received 3,000 cc. In addition sodium bicarbonate was administered

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to most patients. Two routes were utilized to administer the bicarbonate; most patients received 16 Gm. of the sodium salt in 2 Gm. doses orally every twenty minutes; others received 11.25 Gm. dissolved in 500 cc. of distilled water via the intravenous route. When the blood sugar had decreased to 250 mg. per cent, glucose was administered in 25 Gm. portions via the Levine tube; the total dose depended upon the blood sugar level. Shock was treated by administration of plasma and occasionally whole blood.

Potassium chloride was administered parenterally to twelve patients as an isotonic solution (1.14 per cent) in the period following therapy of the acidosis when the serum potassium was low. This solution was given by the oral route in five additional cases. The effect of the administration of potassium chloride was correlated in these patients with the chemical and electrocardiographic findings.

OBSERVATIONS

Alterations in the Serum Potassium in Patients with Diabetic Acidosis. In 1946 Holler[14] reported the occurrence of a low serum potassium accompanied by clinical manifestations associated with the "syndrome of hypopotassemia"* during the treatment of a patient with diabetic acidosis. Administration of potassium to this patient reversed the respiratory distress, flaccid muscle paralysis and the cardiovascular alterations including the electrocardiographic changes.

Atchley, Loeb, Richards, Benedict and Driscoll,[16] Butler, Talbot, Burnett, Stansbury and McLachlan[17] have shown that the *total body* potassium concentration is below normal before therapy is started in patients with diabetic acidosis. These well established facts concerning the level of the total body potassium are in contrast to the findings of the concentration of the *serum* potassium in patients with diabetic acidosis. Martin and Wertman[15] first showed that the serum potassium was often elevated before insulin therapy was instituted in patients with diabetic acidosis.

Figure 1 indicates the findings in the forty-five patients in our series with diabetic acidosis. The serum potassium level is plotted against the hours before and after therapy was instituted. It will be noted that before therapy the serum potassium level varied from a normal concentration of 5 mEq. to a markedly elevated concentration of 9.3 mEq. Thus, in spite of a low total body potassium concentration before therapy in patients with diabetic acidosis, the serum level of this cation is found to be normal or elevated.

On the other hand, as can also be observed from Figure 1, as early as two hours after the first injection of insulin, but more commonly between the third to eighteenth hour, the serum potassium level rapidly drops to a concentration below normal. This observation was constant throughout our study and is of particular importance since it is at this time that the blood sugar level and the carbon dioxide combining power approach normal limits. The clinical condition of the patient at this time was often more critical than before therapy was begun. Also, as will be shown later, the electrocardiogram, which on initial study presented a normal configuration or one usually associated with a high serum potassium, presented the typical findings associated with a low serum potassium. Finally the data of Figure 1 show that the serum potassium levels in these patients remained below normal unless potassium chloride or a diet other than glucose was administered.

* The "syndrome of hypopotassemia" is used to refer to the clinical syndrome which manifests itself in patients with familial periodic paralysis[24–26] and diabetic acidosis.[14,17,28] The signs and symptoms which occur when the potassium of the body is depleted are limited to disturbances in the skeletal muscle and cardiovascular system.

During a crisis all of the striated muscle of the body becomes flaccid. Patients show a gasping type of respiration due to paralysis of the diaphragm and intercostal muscles. The respiratory paralysis may result in death of the patient. The cardiovascular manifestations have been best described by Frenkel.[28] They include such signs and symptoms as an increase in the pulse pressure, low diastolic blood pressure, collapsing pulse, increase in cardiac dullness, systolic murmur, high venous pressure and profound electrocardiographic alterations. Administration of potassium to these patients by the oral or intravenous route results in the disappearance of all signs and symptoms.

Electrocardiographic Findings Associated with High and Low Serum Potassium Levels. The typical electrocardiographic findings usually associated with a high and low serum potassium concentration are shown in Figure 2. The serum calcium (total and ionized) was normal when both tracings were taken. The electrocardiographic changes associated with an elevated serum level of potassium have been described by Winkler, Hoff and Smith[18] in dogs, by Keith, Burchell and Baggenstoss[19] in patients with uremia and by Martin and Wertman[6] in patients with diabetic acidosis. The upper tracing in Figure 2 shows the findings characteristically present in a patient with diabetic acidosis before therapy. The serum potassium level was elevated to 7.3 mEq. The T wave is seen to be increased in amplitude with a narrow base. The Q-T interval[23] is not prolonged.

The electrocardiographic pattern associated with a low serum potassium was described initially by Stewart, Smith and Milhorat[20] in patients with familial periodic paralysis. The electrocardiographic findings in patients with diabetic acidosis were described in 1937 by Bellet and Dyer;[5] recently these changes have been attributed to a low concentration of potassium by Holler[14] and Martin and Wertman.[6] Similar changes have recently been observed by us in patients with intestinal obstruction.[21] The lower tracing in Figure 2 is illustrative

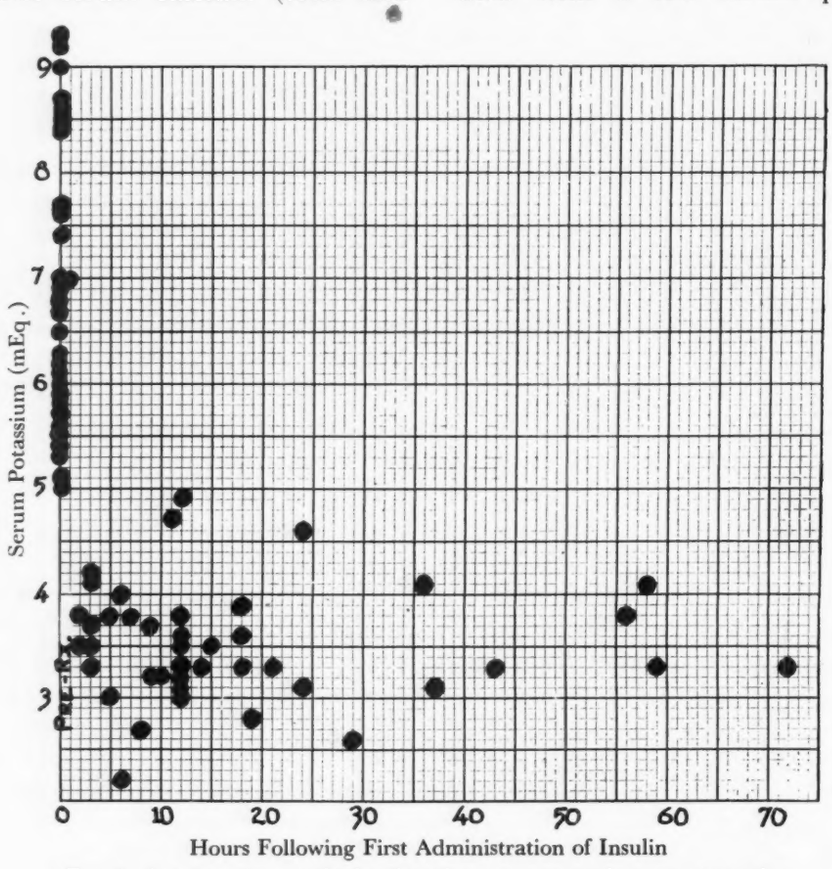

FIG. 1. A composite graph showing the serum potassium concentration of forty-five patients with diabetic acidosis. The serum potassium levels are plotted against the hours following the first administration of insulin. Before therapy the serum level of this cation is normal or elevated. In the period of two to eighteen hours after treatment was instituted, the serum potassium had decreased to levels below normal. The serum potassium did not return to normal until potassium chloride or a diet other than glucose was administered.

of the typical configuration found when the serum level was decreased to 3 mEq. at the time the tracing was obtained. The Q-T interval[23] is now prolonged and the T wave is inverted. These findings, with minor modifications, were constantly present throughout our study of patients with diabetic acidosis.

Effect of the Serum Potassium on the Q-T Interval. Correlation studies: Since the Q-T interval was found to be constantly prolonged after treatment had been instituted in those with diabetic acidosis and since this change appeared to be reversible, the etiology of this finding was investigated. Correlation studies were made of the percentage of increase above normal in the duration of the Q-T interval and the serum levels of certain of the electrolytes. The best relationship is found to exist between the percentage above normal in the duration of the Q-T interval and the serum potassium concentration. Figure 3 shows that a high coefficient of correlation,[29,30] namely, minus 0.73 is found between the percentage of increase in the Q-T interval above normal and the serum level of this cation. When a partial coefficient of correlation[29,30] was determined, keeping the serum calcium normal, the coefficient value was minus 0.92 which is highly significant.

Since the Q-T interval is known to be influenced to a large degree by the heart rate, the serum potassium level was compared with the Q-T interval at a time when the cycle length was constant. It will be noted (Fig. 4) that a high degree of correlation was found. These studies suggest that a definite relation exists between the serum potassium and prolongation of the Q-T interval. Further studies are needed to elucidate the cause of this relationship.

In the patients studied the coefficient of correlation[29,30] was determined also between the percentage of increase in the duration of the Q-T interval above normal and the serum calcium level and between the former and the carbon dioxide tension. In neither case was the relationship significant.

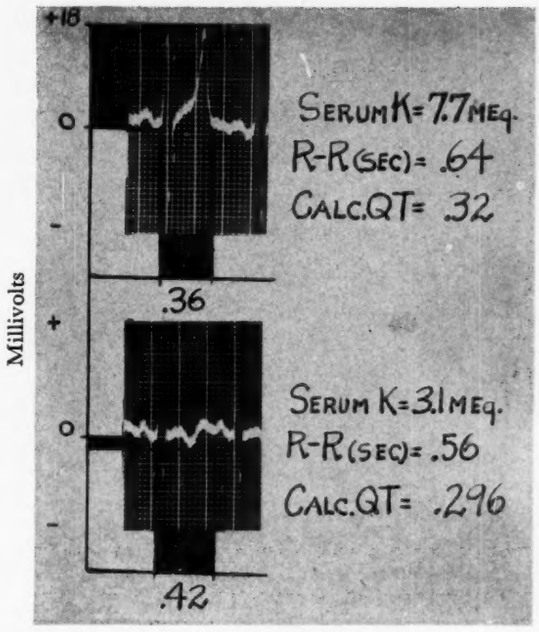

FIG. 2. Electrocardiographic records taken on patient with diabetic acidosis in the precordial lead CR_3. The upper tracing was obtained before therapy was instituted at which time the serum potassium level was elevated. The lower tracing was taken a short time after treatment was begun when the serum potassium had decreased to a level below normal. The serum calcium (total and ionized) was normal when both electrocardiograms were obtained.

Effect of Intravenous Potassium on the Q-T Interval. In an effort to study the effect of the serum potassium concentration on the Q-T interval, potassium chloride was administered to patients with diabetic acidosis at a time when the electrocardiogram showed changes suggestive of a low serum potassium. Figure 5 is illustrative of a typical instance. It will be noted that when the serum level of this cation has decreased to 4.4 mEq., the Q-T interval was prolonged by 23 per cent above the calculated normal value. After administration of 450 cc. of potassium chloride (isotonic solution), the Q-T interval became normal in duration. More important was the observation that when 50 cc. of potassium chloride were administered quickly, namely, in seven minutes the Q-T interval rapidly became shorter in duration. This figure also shows that shortly after the potassium chloride was discontinued the

Q-T interval, which had been normal, rapidly became prolonged. This finding was constant in the twelve patients studied in this manner. Since these observations indicate that the Q-T interval underwent alteration at a time when the potassium level in the serum changed, they suggest that the duration of electrical systole (Q-T interval) is influenced to a great extent by the serum potassium level in patients with diabetic acidosis.

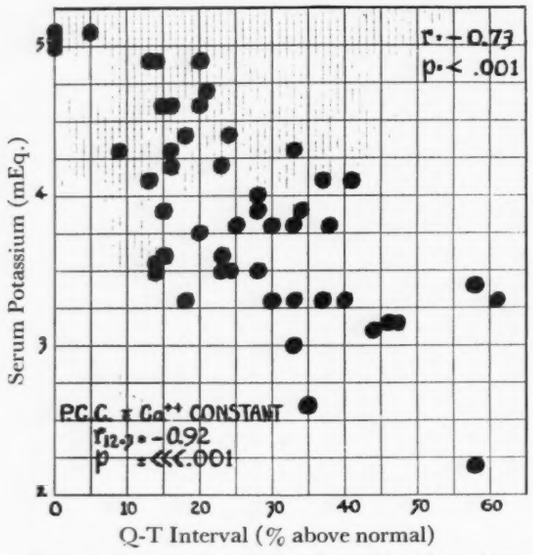

FIG. 3. Composite graph of results taken from forty-five patients with diabetic acidosis. The serum potassium level is compared to the percentage above normal in the duration of the Q-T interval. The coefficient of correlation (r) was minus 0.73; this value indicates that a significant relation exists between these two factors. In the lower left hand corner of this figure the partial coefficient of correlation obtained when the serum calcium was kept constant is represented. The value of minus 0.92 indicates that a highly significant relationship exists between the serum potassium concentration and the percentage above normal in the duration of the Q-T interval when the serum calcium is kept constant.

The possible relation of changes in intracellular potassium to alterations in the Q-T interval must be considered at this point. Since it has been found that the potassium which disappears from the serum cannot be accounted for in the urine or feces, it is logical to assume that it enters the intracellular compartment. Changes in intracellular potassium could not have caused these alterations in the Q-T interval since this cation would be increasing inside the cell both during the administration of potassium chloride and after it had been discontinued.

The Q-T interval may also be prolonged by a low serum calcium.[22] In hypocalcemia the T wave itself is not involved in the prolongation of the Q-T segment; this is due entirely to lengthening of the isoelectric period between the end of the QRS and the beginning of the T wave. In hypopotassemia, however, prolongation of the Q-T interval involves the T wave proper which is widened. (Fig. 5.)

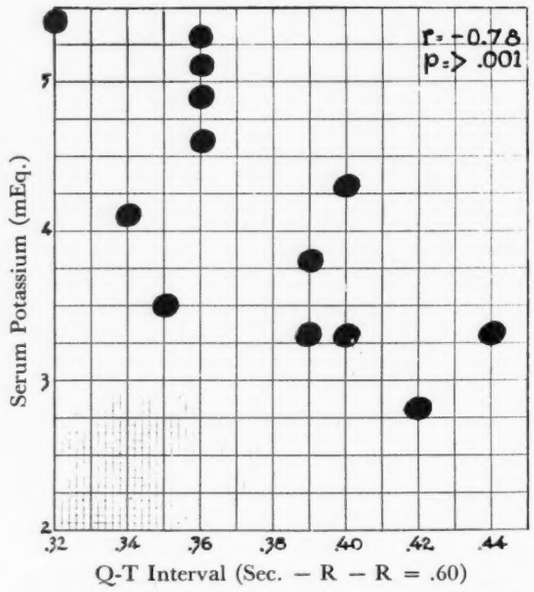

FIG. 4. Composite graph showing relation of serum potassium and Q-T interval in patients receiving active therapy for diabetic acidosis when the heart rate or cycle length (R-R) is kept constant. When the coefficient of correlation (r) was determined, a value of minus 0.78 was found indicating a highly significant relationship exists between these two factors.

These results differ from those reported by Martin and Wertman[6] who found that in only 43 per cent of their patients with prolonged Q-T interval could the prolongation be explained by a concomitant low serum concentration of potassium or calcium. We found in our group of patients that the serum calcium (both total and ionized) was decreased only in the few in-

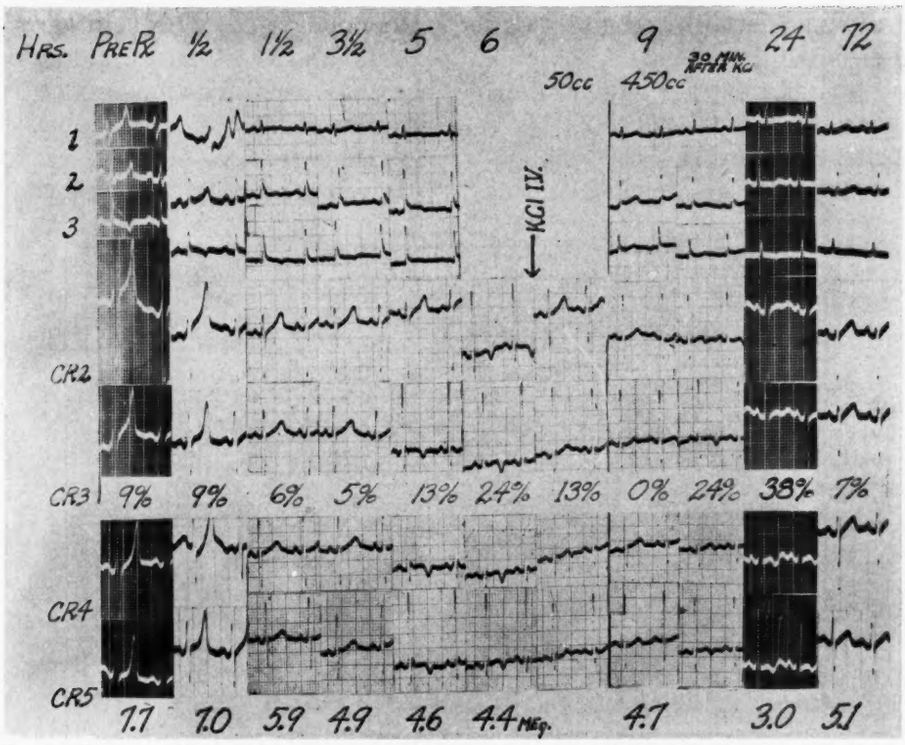

FIG. 5. Electrocardiographic records of leads 1, 2, 3 and precordial leads CR_2, CR_3, CR_4 and CR_5 taken in a patient before and after institution of routine therapy for diabetic acidosis and before and during administration of isotonic potassium chloride. Numbers in the upper part of the figure record the hours after routine therapy was begun. The arrow indicates the time when isotonic potassium chloride was started. The percentage values in the center of the figure represent the calculated percentage of increase above normal of the Q-T interval in the CR_3 position. Numerals under each tracing in the lower part of the figure record the serum potassium level in millequivalents at the time the tracing was taken.

stances when the patients had been in alkalosis for a period of forty-eight hours or longer; when alkalosis existed, the serum potassium level, in addition to the serum calcium concentration, was below normal. Electrocardiograms taken at this time showed a more marked prolongation of the Q-T interval than was found when the potassium concentrations alone were decreased. Additional proof that the level of serum calcium (total or ionized) does not influence the prolongation of the Q-T interval to a great extent in the patients who form the basis for this report is our observation that in five cases intravenous administration of calcium gluconate did not shorten the Q-T interval at a time when it was prolonged.

One other point is deserving of emphasis: the changes in the Q-T interval are most characteristic in the precordial leads in contrast to the limb leads. The T waves are often isoelectric in the limb leads when the Q-T interval is prolonged, making it difficult to measure the length of electrical systole. Of the precordial leads CR_3 has proved to be the most informative.

Factors Related to the Height of the T Wave. Correlation studies: The relationship between the height of the T wave and certain constituents of the blood was investigated. Figure 6 shows that a highly significant correlation existed between the height of the T wave and the blood pH. Correlation of the serum potassium concentration and the height of the T wave was significant only when the plasma concentrations of this cation were elevated. Figure 7 shows, however, that a significant correlation was found when the height of the T wave and the carbon dioxide tension was analyzed in these patients. Since changes which affect

the carbon dioxide tension and the blood pH are determined by alterations which occur both intra- and extracellularly, these findings suggest that the height of the T wave is probably controlled by changes which take place both inside and outside of the myocardial cell at any given time. This is a very complicated mechanism and a more detailed explanation must await further study.

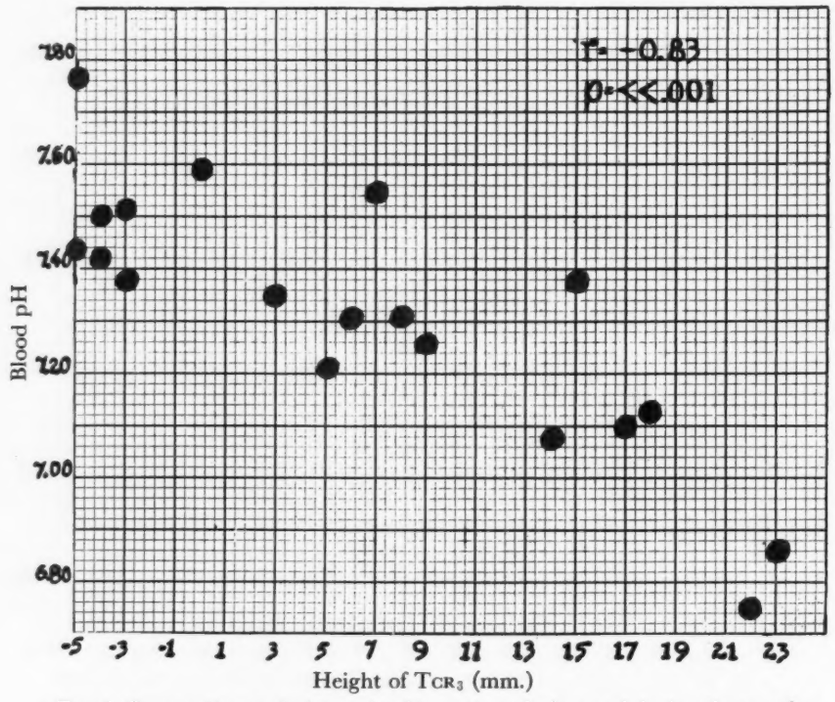

FIG. 6. Composite graph determined in patients before and during therapy for diabetic acidosis. The blood pH is compared to the height of the T wave in millimeters as found in precordial lead CR_3. The coefficient of correlation value (r) was minus 0.83, indicating that a highly significant relationship exists between these two factors.

Effect of Intravenous Administration of Potassium Chloride on the Height of the T Wave. In spite of the poor quantitative relation between the serum potassium and the height of the T wave, observations on the effect of intravenous potassium chloride indicate that a definite qualitative relationship exists. When the serum potassium was found to be elevated, the T wave was tall with a narrow base. In contrast, when the serum potassium level was below normal the height of the T wave in patients with diabetic acidosis was diminished in amplitude or inverted. This is in agreement with Martin and Wertman[6] who found that some correlation existed between decreased amplitude of the T wave and low serum potassium levels.

A typical example of the behavior of the T wave during administration of potassium chloride is shown in Figure 8. When the T wave was inverted or of diminished amplitude, administration of isotonic potassium chloride increased the height of the T wave. When the serum potassium level became normal, the height of the T wave assumed a normal amplitude. Since this finding was so constant throughout our study, we believe that for practical purposes it can be said that during treatment of patients with diabetic acidosis if the Q-T interval is found to be prolonged, the level of the serum potassium can be crudely estimated from the height of the T wave.

Relationship of the U Wave to Serum Potassium. In a small group of patients with

diabetic acidosis a U wave was found in the electrocardiogram when the serum potassium level was below normal. To our knowledge the U wave has not been previously emphasized as being related to changes in the electrolytes. This relation with diabetic acidosis was first described by Bellet and Dyer.[5] They observed that this occurred after therapy had been instituted, at which time the Q-T interval was prolonged and the T wave inverted. This would indicate that the S-T segment

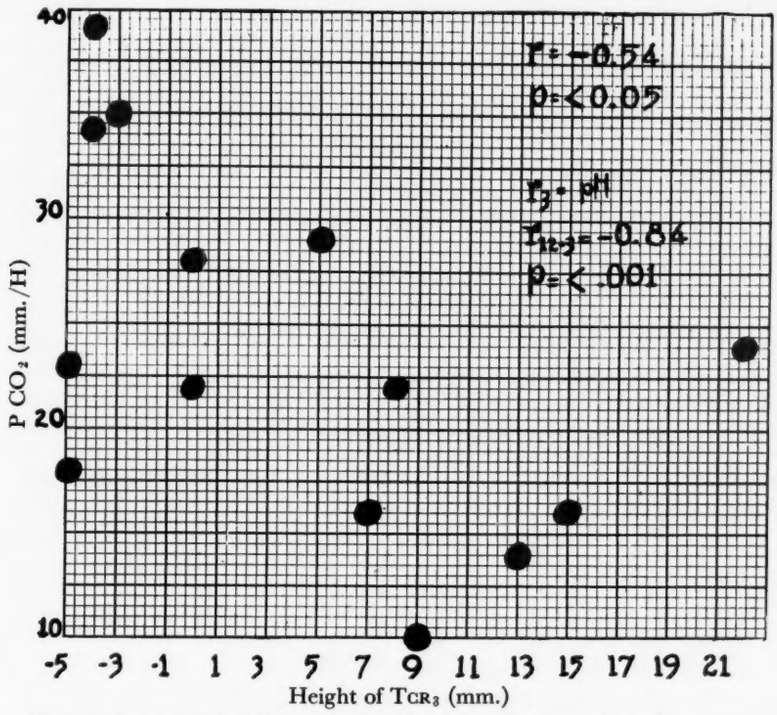

FIG. 7. Composite graph representing the relationship of the carbon dioxide tension and the height of the T wave in the precordial lead CR_3 in patients with diabetic acidosis. The coefficient of correlation value of minus 0.54 indicates that a significant relationship exists between these two factors. There is admittedly a large source of error in these carbon dioxide tension figures since the carbon dioxide combining power was used in lieu of the total carbon dioxide valences in determining the carbon dioxide tensions. The nomogram of Van Slyke and Sendroy[31] was used to determine the carbon dioxide tensions on these patients.

may be relevant in two ways. (Fig. 8.) First, a U wave when present often made it difficult to measure the Q-T interval since it masked the end of the T wave. Second, a U wave which was present when the serum potassium concentration was below normal completely disappeared during intravenous administration of potassium chloride. This finding was constant throughout our study and suggests that the U wave in these patients was related in some way to a disturbance in the electrolytic balance.

Factors Related to the S-T Segment Depression. Depression of the S-T segment in patients depression is related in some way to the serum potassium level. Undoubtedly, some relationship may exist; however, about 50 per cent of the patients in our series showed no S-T segment depression when the serum potassium was below normal. Further investigation indicated that the S-T segment depression was related to the degree of cardiovascular shock present in a large group of these patients. Figure 9 is a typical instance. It will be noted that the S-T segment was isoelectric when the serum potassium level was normal and elevated. Six hours after therapy the blood pressure

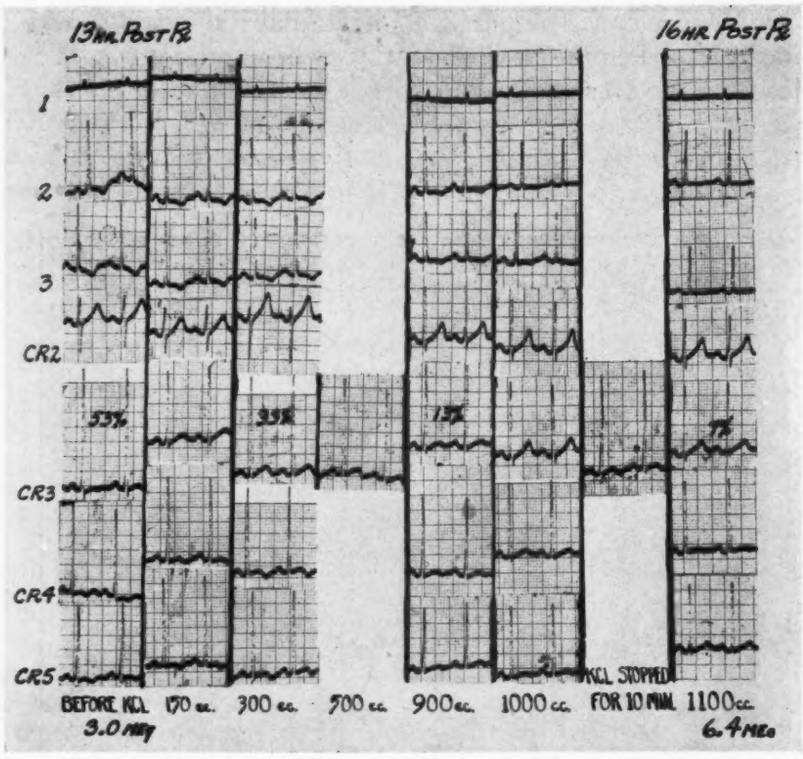

FIG. 8. Electrocardiographic tracings taken before and during the administration of 1,100 cc. of isotonic potassium chloride to a patient being treated for diabetic acidosis. The first tracing was taken thirteen hours after the initial routine therapy for acidosis had been instituted. The serum potassium level was decreased to 3.0 mEq. A tracing was taken after 150 cc., 300 cc., 500 cc., 900 cc., 1,000 cc. and 1,100 cc. of potassium had been administered. The figure shows that the T waves which were inverted in precordial leads CR_3, CR_4 and CR_5 became normal in amplitude after a liter of potassium chloride had been administered and the serum potassium level had risen to the top normal value of 6.4 mEq. Also to be observed is the U wave present in precordial lead CR_4 when the serum potassium level was below normal which disappeared during the administration of potassium chloride. The percentage numbers in the center of the figure represent the percentage above normal in the duration of the Q-T interval at the time the tracing was taken.

decreased to 90/70 and the S-T segment became depressed. Five hours later the blood pressure was 90/38 and the S-T segments were further depressed. The serum potassium level was 4.1 mEq. at this time. During the administration of potassium chloride it will be noted that the blood pressure returned to normal and the S-T segment became isoelectric.

SUMMARY

1. In a study of forty-five patients with diabetic acidosis the serum potassium level was found to be normal or elevated before therapy and fell to concentrations below normal soon after treatment was instituted.

2. Studies are presented which suggest that the duration of the Q-T interval is influenced for the most part by the level of serum potassium in these patients.

3. There was a significant correlation between the height of the T wave and the blood pH and carbon dioxide tension.

4. The height of the T wave is undoubtedly influenced by the serum potassium level. The relationship is only qualitative and in no sense quantitative. Studies are presented which suggest that only in the presence of prolongation of the Q-T interval, when the S-T segments remain normal in duration, can the height of the T wave be used as a crude means of estimating the serum potassium level in patients who are actively treated for diabetic acidosis.

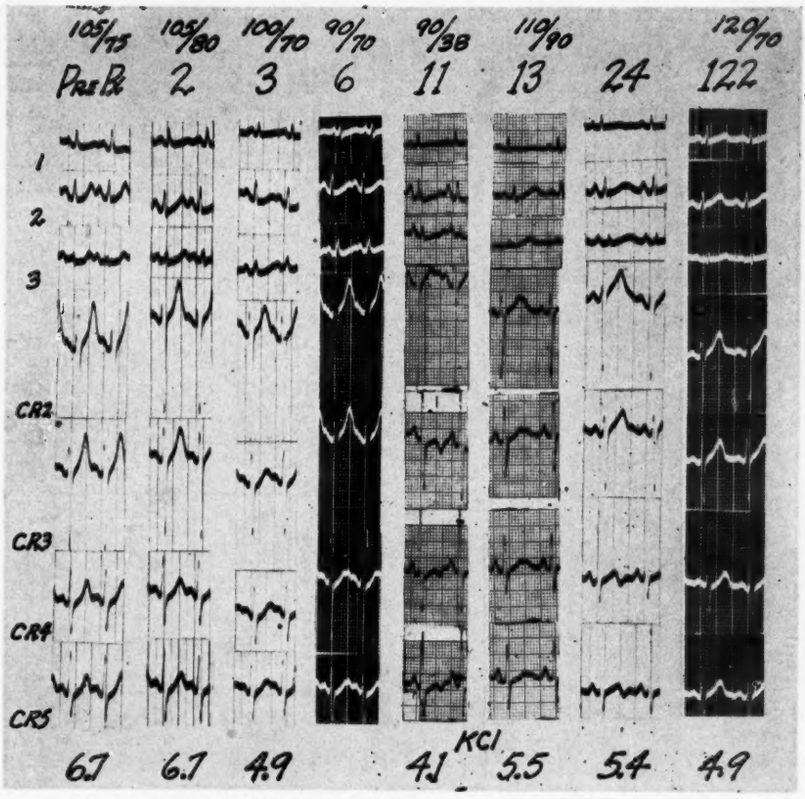

FIG. 9. Electrocardiographic tracings taken in a patient before and during treatment for diabetic acidosis. The top numbers are blood pressure readings taken at the same time the tracing was obtained. Beneath these readings are recorded the hours after routine therapy was begun. At the bottom of the figure the numbers indicate the serum potassium level in millequivalents. Between the eleventh and thirteenth hour 300 cc. of isotonic potassium chloride were administered.

5. The appearance of a U wave in the electrocardiogram when the serum potassium concentration was below normal is described. Such U waves consistently disappeared during administration of isotonic potassium chloride.

6. Since the configuration in the electrocardiogram in these forty-five patients with diabetic acidosis was consistently related to the level of serum potassium, we believed that this instrument offers a valuable means of following in a crude way the serum potassium level during the treatment of patients with diabetic acidosis.

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Sponge Biopsy in Cancer Diagnosis*

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THE histologic diagnosis of cancer is based on surgical biopsy involving surgical removal of a block of tissue from the suspected organ. Efforts toward a cytologic diagnosis of cancer have received considerable stimulus from the extensive and valuable studies of Papanicolau and Traut[1] who demonstrated the usefulness of the cytologic examination of vaginal secretions for the presence of tumor cells in the diagnosis of uterine and especially of cervical cancer.

Certain shortcomings have become apparent in the vaginal smear technic for cancer diagnosis. First, certain tumors, such as adenoma malignum, exfoliate few if any cells into the vaginal secretions. Second, when very few cells are present, a prolonged search of the smear, up to two hours, may be necessary before they are found. Third, the tumor cells form a very small proportion of the total number of cells in the smear, the latter arising from the varied epithelial and glandular surfaces of the female reproductive tract. Fourth, the cells of the vaginal smear have all been exfoliated at an uncertain time prior to the collection of the specimen and have undergone various necrobiotic and autolytic changes leading to many atypical shapes and forms which may be confused with tumor cells or render distinction possible only after considerable special training and experience on the part of the examiner. Fifth, the Papanicolau technic calls for use of an additional series of fixatives and stains beyond those customarily used in routine pathology laboratories.

DESCRIPTION OF THE SPONGE BIOPSY METHOD

The present method represents a simplified technic for obtaining living cells and clumps of cells in a form suitable for paraffin embedding directly from the tissue suspected. It consists essentially of rubbing a small piece of sponge over the suspected tissue. Fluid and cells exuding from the tissue will be absorbed by the sponge which is then dropped into a small bottle of 10 per cent formalin or other fixative as preferred. The sponge and its absorbed contents are then treated as one would treat a block of tissue for embedding, cutting and staining (hematoxylin and eosin) prior to microscopic examination. A sponge of protein composition such as gelatin is particularly suitable for this purpose because it does not dissolve in the various solvents used in tissue preparation, it has good absorptive powers and is easily cut with the tissue microtome. In our experiments we have used Gelfoam No. 12.* A flat square of sponge 2.0 by 2.0 by 0.5 cm. is clamped along one margin by a surgical sponge forceps. After insertion of a vaginal speculum and visualization of the cervix the sponge is rubbed firmly over the mucosal surface and muco-epithelial junction of the external os to insure liberation and absorbtion of sufficient material for examination. Each of the two flat surfaces of the sponge is thus rubbed over the tissue so that after fixation and paraffin embedding either surface of the block may be used in sectioning.

It may be seen that the method described attempts to overcome the shortcomings of the vaginal smear technic. The present procedure does not await exfoliation of cells. The latter individually or in clumps are rubbed off and absorbed from the tumor itself. Second, the number of tumor cells

* Manufactured by The Upjohn Company.

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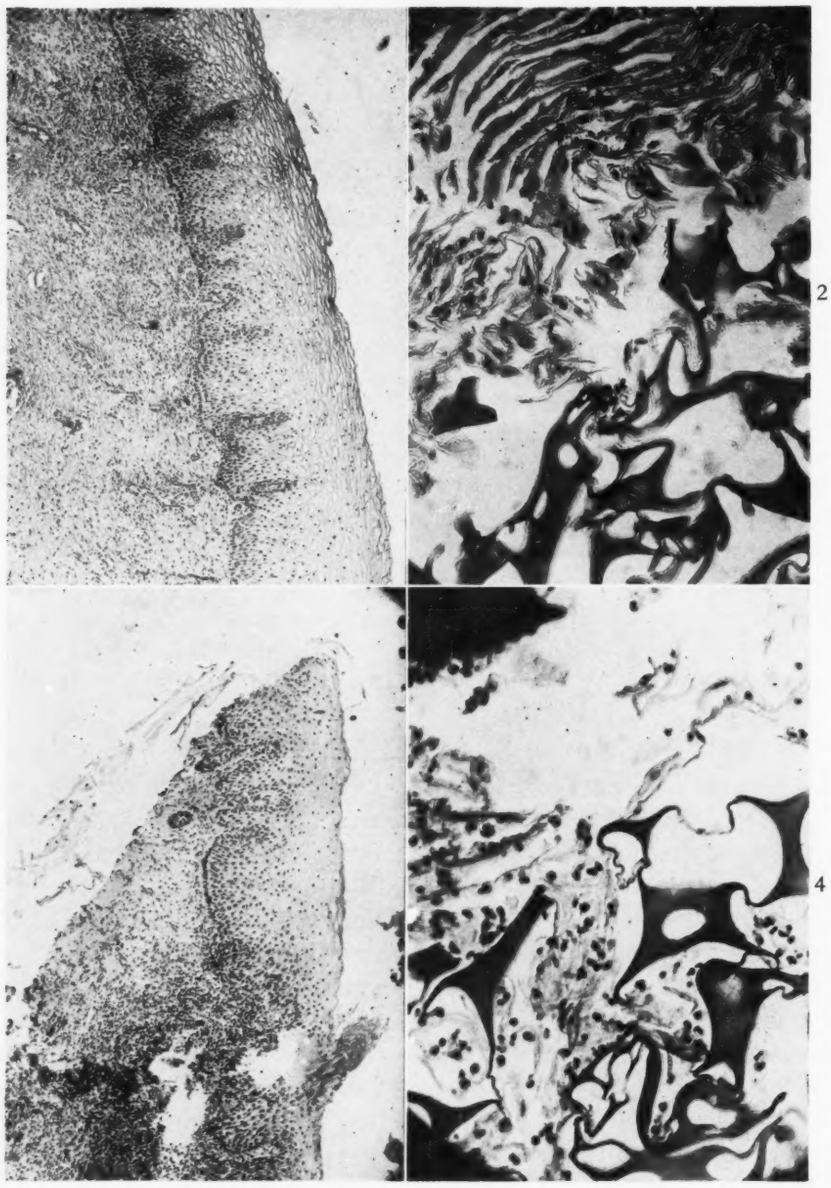

FIG. 1. Surgical biopsy of normal cervix uteri showing surface of stratified epithelium with underlying vascularized fibromuscular tissue. × 100.

FIG. 2. Sponge biopsy of normal cervix (same as Figure 1). The thick, dark strands below represent the gelatin structure of the sponge. Adherent above and in the interstices of the sponge are masses of stratified squamous cells, mostly of the superficial type. × 440.

FIG. 3. Surgical biopsy from cervix showing many inflammatory cells in both superficial and deep zone. × 100.

FIG. 4. Sponge biopsy of inflamed cervix (same case as Figure 3). A few epithelial cells, mucus, and many leukocytes, mononuclear and polymorphonuclear cells are seen. × 440.

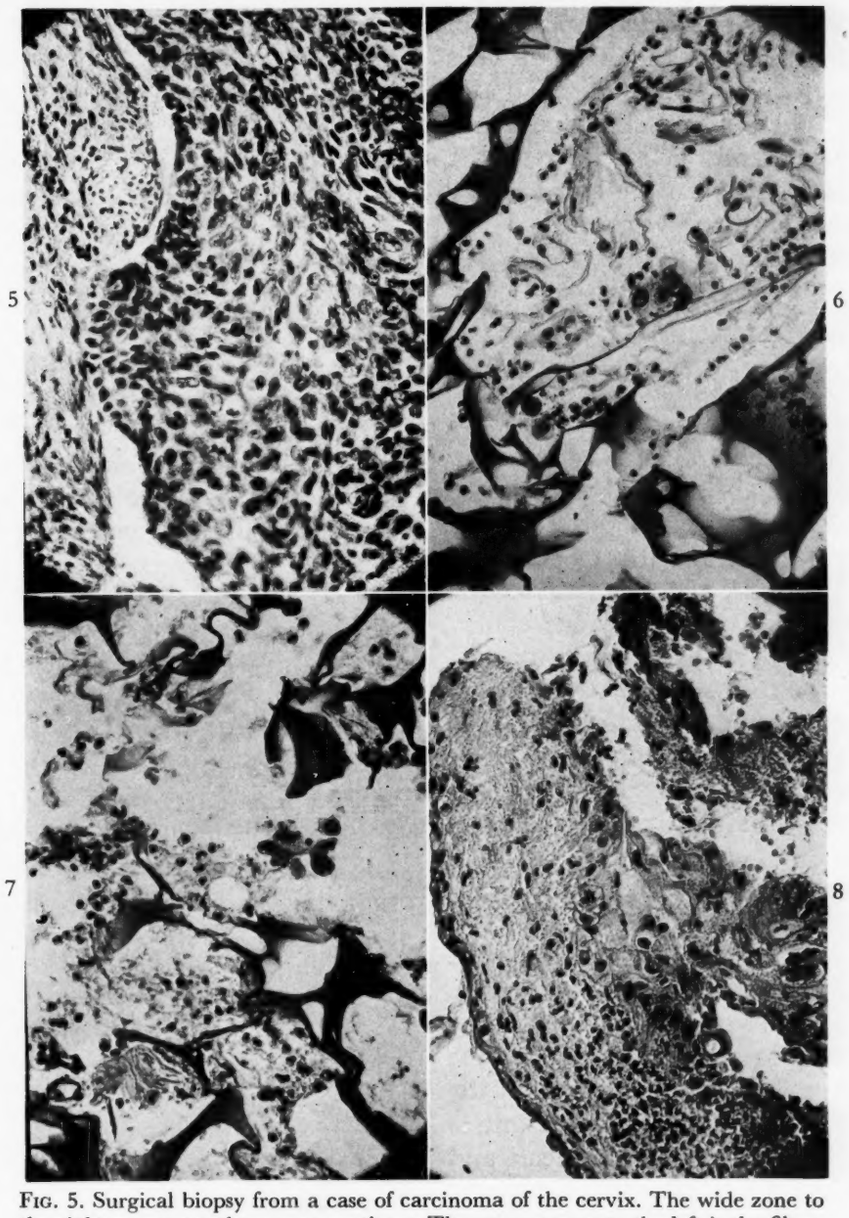

FIG. 5. Surgical biopsy from a case of carcinoma of the cervix. The wide zone to the right represents the cancerous tissue. The narrow zone to the left is the fibromuscular tissue of the cervix. Note the large, irregular, darkly-staining tumor cells. × 440.

FIG. 6. Sponge biopsy from same case as Figure 5. In the center of the field is a clump of four tumor cells. Below and to the left are two more tumor cells. Also present are numerous epithelial cells and leukocytes. Note the large size of the tumor cells as well as their nuclei in comparison with the leukocytes. × 440.

FIG. 7. Sponge biopsy from same case as Figure 5. To the right of center is a group of five tumor cells. Epithelial cells, leukocytes and outlines of erythrocytes are also present. × 440.

FIG. 8. Sponge biopsy from same case as Figure 5. A small tissue fragment adherent to the sponge is shown. Below and to the left are inflammatory and necrotic areas. In the center and to the right is a mass of viable tumor tissue. Note the bizarre shapes and large size of many nuclei. Just to the left of center is a nucleus in mitotic division. × 440.

collected is greatly increased and permits of ready detection. Third, practically all cells included are obtained from the tissue under examination. There is practically no admixture of extraneous cells. Fourth, the cells are living cells which are immediately fixed, avoiding disintegrative changes. Fifth, the method employs routine fixatives and stains.

RESULTS

We have examined eighty-eight slides from sponges rubbed over tumorous and non-tumorous tissues. In general the tumor cells when present are so numerous and so readily recognized as to permit prompt diagnosis. The cells are well preserved and well fixed. They show the characteristic changes, large size of cells and nuclei, marked variations as to shape and size, hyperchromatism, anaplasia, atypism and occasional mitoses. Even in the absence of tumor cells the sponge biopsy will give useful information regarding the physiologic or pathologic condition of the surface examined.

The figures represent a series of photomicrographs comparing the findings in sponge biopsy with those of surgical biopsy. (Figs. 1 to 8.) In the normal cervix the sponge merely takes up clumped and individual stratified squamous cells from the mucosal surface. In the inflamed cervix the sponge takes up a considerable amount of mucus with enmeshed mononuclear and polymorphonuclear leukocytes. Epithelial cells, mostly of the superficial type with an admixture of a few cells from the intermediate and deeper epithelial layers, are also found.

In the cancerous cervix the sponge takes up tumor cells individually or in clumps and occasionally small fragments of tumor tissue. The cells are large, irregular, with large, darkly-staining nuclei, sometimes multiple and occasionally in mitosis. Seen in groups or singly, as illustrated, they are readily recognized. Since these tumors are usually ulcerated and infected, one finds leukocytes, polymorphonuclear and mononuclear in type, mucus and erythrocytes. Squamous cells are also present.

COMMENT

The simplicity of the method in respect to gathering, handling and examination of material is such as to encourage further trial. The procedure is adapted to the microscopic examination of the cellular composition of mucous membranes, ulcerative membranes, neoplastic membranes, etc. It is especially useful in the diagnosis of carcinoma of the cervix and may prove applicable in the study of other mucous membranes, e.g., the mouth and pharynx, esophagus, bronchi, rectum, etc.

SUMMARY

A method of sponge biopsy in cancer diagnosis is presented. It consists essentially of absorbing fluid cells and particles of tissue expressed from the surface of a mucous membrane or ulcerating lesion in a suitable sponge. Sponge and contents are treated as a tissue block for fixing, embedding, cutting and staining prior to microscopic examination. The results of sponge biopsy compared to surgical biopsy are illustrated. The method appears to be applicable in the diagnosis of carcinoma of the cervix and may prove applicable in the study of lesions of other mucous membranes that may be reached with a sponge.

ADDENDUM

Subsequent to the completion of this report, the author has successfully applied the method of sponge biopsy in cases of adenocarcinoma of the rectum and sigmoid colon, carcinoma of the corpus uteri, bronchogenic carcinoma of the lung, epidermoid carcinoma of the skin, etc. These lesions were reached by the sponge as required through the proctoscope and sigmoidoscope, vaginal speculum and bronchoscope. Details of procedure and microscopic findings will be published at a later date.

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Use of Intermittent Positive Pressure Breathing Combined with Nebulization in Pulmonary Disease*

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BARACH and his associates[1–3] and others[4] have demonstrated the usefulness of aerosols in the treatment of pulmonary disease. The methods of administration that have been used depend largely on the inspiratory effort of the patient to carry the aerosol into the lungs. However, in some patients adequate dissemination of aerosol may be prevented by physical limitations of breathing, such as obstruction, emphysema, fibrosis and impaired movement of the diaphragm. In the present study an automatic intermittent positive pressure breathing respirator has been combined with a nebulizer for administration of vasodilator agents, penicillin and other substances suitable for nebulization. Since intermittent positive pressure breathing increases both the minute volume of ventilation and the respiratory excursions, it seemed likely that the vapor from a nebulizer employed with this type of breathing apparatus would be more uniformly distributed through the lung air spaces than by methods dependent on the inspiratory effort of the patient alone. Better dissemination of the aerosol would be expected, particularly in individuals with poor diaphragmatic excursions and shallow breathing. If accumulated secretions block the bronchi and bronchioles, intermittent positive pressure breathing may loosen the plugs and promote drainage.

Intermittent positive pressure breathing (IPPB) as produced by automatic respirators consists of active inflation of the lungs under positive pressure (above atmospheric) during inspiration and of passive deflation during expiration, primarily produced by the elasticity of the lungs and chest wall. The peak mask pressure varies with the line pressure which is adjustable from 0 to 30 cm. of water. When the peak mask pressure is reached, cycling of the respirator interrupts the applied positive pressure and opens the expiratory pathway to atmospheric pressure. The IPPB used in this study produces a small decrease in cardiac output,[5–7] but this reduction is less than that which normally occurs in man when changing from the supine to the standing position. Changes in blood pressure in the systemic arteries, right ventricle and pulmonary artery are of small magnitude, there usually being a slight elevation of the mean pressure in each. Hyperventilation may occur with IPPB, but lowering of the arterial pCO_2 can be controlled.[8] Tetany or its prodromal signs have not been observed during IPPB.[5,7,8] In patients with physiologic hypoventilation a lowering of the arterial pCO_2 with IPPB indicates an increase in the volume of effective alveolar air.

A pneumatic balance type respirator,[5] which can be seen in the accompanying

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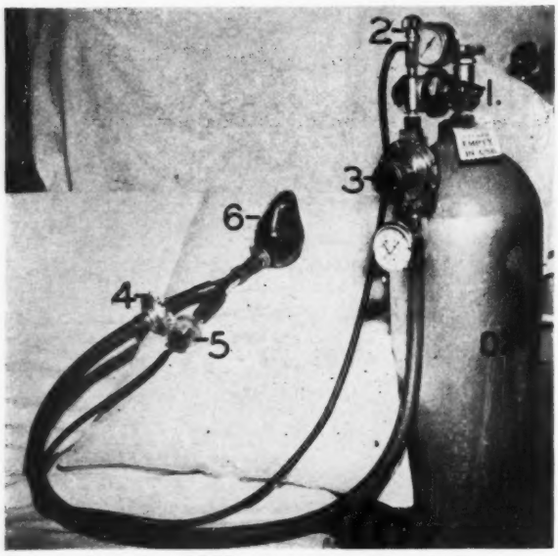

FIG. 1. Complete IPPB apparatus with nebulizer connected. (1) Pressure reduction valve on a high pressure oxygen cylinder; (2) needle valve for supplying pressure to the nebulizer; (3) line pressure valve with an adjustable range from 0 to 30 cm. water; (4) pneumatic balance type respirator; (5) special nebulizer used with the IPPB apparatus; (6) oxygen mask.

illustration, was used to provide IBBP* in the present study. This device is a simple differential pressure valve which changes continuous positive pressure (adjustable from 0 to 30 cm. of water by the regulator on the oxygen cylinder) into an intermittent positive pressure, thus functioning as a respirator capable of producing effective artificial respiration in the apneic subject (6 to 10 liters per minute).[5] In this study the line pressure of the IPPB apparatus was set at 20 cm. of water. This respirator follows the slightest breathing effort of the conscious subject and unlike most automatic respirators the cycling pattern is not fixed. These features permit easy, comfortable and almost effortless breathing in the conscious patient if a suitable type face mask be used.

A nebulizer (seen in the illustration) was constructed of heavy clear plastic with a stainless steel nebulization mechanism which could be removed for cleaning and adjustment. Other nebulizers commercially available, although more fragile and difficult to clean, can be used with this arrangement. The gas pressure for operating the nebulizer was obtained by connecting a needle valve, between the first and second stage reduction valves on the oxygen regulator of the IPPB apparatus, with a piece of small-bore rubber tubing to the nebulizer. (Note photograph.) This arrangement provided a controllable pressure greater than the line pressure used for the IPPB and thus prevented backflow in the nebulizer during inspiration. The nebulizer pressure was regulated so that the cycling characteristics of the respirator were not altered and the IPPB as provided by the respirator was not hampered.

The nebulizer provides humidification of dry oxygen or other gases when IPPB is used for several hours or more. Pharyngeal irritation by dry gases has been previously reported[8] as a limiting factor to prolonged application of IPPB in apneic patients or in those with respiratory depressions of various types. The use of dry gas for one hour or more may produce annoying throat irritation in some conscious patients. Humidifiers previously designed for use with IPPB apparatus have been bulky and cumbersome while the nebulizer is small, compact, portable and easy to operate. For prolonged IPPB in patients with or without spontaneous respirations water should be used in the nebulizer at frequent intervals unless there is some distinct contraindication to moisture such as pulmonary edema.

Twenty-six patients with silicosis, emphysema and dyspnea, with and without superimposed bronchial infections, have been treated by the IPPB nebulizer method. All patients received a course of treatment of one to two weeks' duration, consisting of four fifteen minute applications per day of IPPB using 100 per cent oxygen and 1.5 cc. of 0.5 per cent neosynephrine in the nebulizer. Secondary reactions have not been noted from the use of 1.5 cc. of 0.5 per cent neosynephrine administered in this manner. Use of penicillin in concentra-

* This apparatus is manufactured by the Mine Safety Appliance Co. (Pneophore was used for producing IPPB.)

tions as high as 50,000 units in 1.0 cc. of saline combined with the aforementioned amount of neosynephrine in patients with superimposed bronchial infection has been satisfactory. Both respirator and nebulizer should be cleaned after each treatment period, especially after using penicillin.

All patients treated thus far have reported some subjective relief consisting primarily of less "tightness" of the chest, "lighter" and easier breathing, decreased secretions and cough, improved appetite and more strength. Usually for the first two or three days after the beginning of treatment the amount of secretions has been increased and frequently, in the anthracite coal miner group, the sputum was black or dark-tinged even though the patient may not have been in a coal mine for several years. After about a week of treatment the secretions dwindled and in some cases totally disappeared. It is probable that the most beneficial effect from IPPB with a vasodilator agent in this group was the promotion of drainage of the bronchi and bronchioles. However, this combination therapy also provides an effective method of treatment during acute respiratory episodes in a group of patients with marked diminution of breathing reserve and with poor respiratory excursions. In silicotic patients the degree of emphysema as evaluated by x-ray is frequently most marked in the lung bases. Fluoroscopy has revealed increased ventilation in the lungs of all patients receiving IPPB, and this increase is especially noticeable at the lung bases in silicotic patients who had limitation of diaphragmatic movement. Pulmonary function studies were made on twenty-five of this series of patients before and after the course of IPPB nebulizer treatment. These studies, including maximal breathing capacity, vital capacity, minute ventilation and the estimation of emphysema (residual air expressed as per cent of total lung volume), showed no significant changes.

In three patients who had repeated attacks of asthma with intercurrent bronchitis, immediate relief was afforded by the combined use of IPPB and neosynephrine or isuprel nebulization. One patient (a physician) reported that relief from the treatment was faster and more effective than epinephrine administered parenterally. The type of IPPB apparatus used here should not be used on a patient in a severe acute asthmatic attack because the instantaneous flow rate is not large enough;[8] however, it can be used after the patient has been given sedatives or the acute attack has subsided.

SUMMARY

The use of IPPB with a nebulizer offers a method by which an aerosol can be distributed in the lungs more effectively in some patients than was usually possible by other technics. Fluoroscopy shows increased ventilation of the lungs, especially at the bases, with IPPB. Since IPPB increases the effective alveolar air, the value of vasodilator substances, chemotherapeutic and antibiotic agents thus administered in pulmonary disease would be enhanced. The combined use of the nebulizer containing an aqueous solution with IPPB apparatus tends to prevent irritation of the throat by the dry gas. In anthrasilicotic patients with dyspnea promotion of better drainage from the bronchi and bronchioles appears to be the most beneficial effect of IPPB combined with a nebulized vasodilator agent.

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Review

Psychosomatic Medicine*

Its History, Development and Teaching

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ONE of medicine's most challenging and necessary tasks today is to correlate the physical and emotional elements of illness, to erect a common ground on which the sciences of medicine and psychiatry may stand together not as contenders for the health of man but as equal partners in its service. No longer need physicians lead a "double life," reserving their confidence in organic diseases for those hours spent in the office or laboratory, but elsewhere living the life of anxious, apprehensive and fearful men. The Hyde, who in his office blandly tells his neurotic patient that there is nothing wrong with him, is a different man from the Jekyll of the home who worries about himself, his family and the future, whose discourses on politics and religion lack the cold scientific reasoning expressed in his consulting room. This divided allegiance between the organic and functional elements of disease is accepted by many who frankly believe that man must live in two worlds and that he should not mix his science with the emotions. Recent studies tend to refute this attitude as unscientific.

One who faces the hard facts of history today, however confident he may be, can hardly say that all is going well with Man. This has arisen from the fact that intellectual achievement as expressed in the progress of science is cumulative and thus has been able to outrun the mental qualities of man. These qualities being so closely involved with instinct and so near the purely biologic level are hard to change.[1]

If one grants the vital necessity of bringing together the two disciplines of mind and body, psychiatry and internal medicine, how best can this be accomplished? Since this is a major task of education, we must look to the Universities to meet the problem. But in the meantime what to do for those physicians who are interested in this "new" concept, who wish to pursue and study it but who find no formal course open to them at this time? Many of the younger physicians have returned from military service with the realization that their training had been entirely too limited in scope.[2] Regardless of their specialties they soon discovered that a high percentage of their medical problems were psychosomatic, and because of lack of training in this field found themselves quite unprepared.

The object of this paper is to survey the development of psychosomatic medicine and to give the writer's experience in the teaching of this subject since 1936, and to present a bibliography which may help the physician in his reading on the subject.

HISTORY

While it is not novel anymore to say that the psychosomatic concept has been known for thousands of years, it is still interesting to record that Socrates over 2500 years chided the Athenian physicians for their organistic medical attitude. He expressed the view that the body could not be cured without treating the mind, that the cure of many diseases was unknown because physicians were ignorant of the whole.[3] Aristotle

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Read in part before the Montreal Medico-Chirurgical Society, March 19th, 1948.

went even further in suggesting that emotions are associated with physiologic responses and that these responses do not correspond in intensity to the emotion since some emotions are subconscious and therefore not evaluated.[4] Thus from the days of the early philosophers, medical science and biology have been struggling to find an integrative formula, an approach which would offer both a methodologic unity and an empirical coherence to our clinical studies.[5]

It was the generation of German medicine in the middle of the nineteenth century which was particularly keen in its search for a new and more scientific understanding of medico-psychologic problems. Those concerned with psychosomatic medicine today owe a great deal to that generation, particularly to Nasse and Jacobi. Nasse sought not only to understand the relationship between mental illness and the physiologic economy but introduced an original note which is particularly familiar to the present day psychiatric clinician. He reported that any physical disease produces a disturbance in the relationship between the psyche and the soma. In 1838, Jacobi published a paper entitled "Further discussions of the foundation of somato-psychic medicine." This would seem to be the first medical formulation of the concept of the intent of psychosomatic medicine which is therefore over a century old.

However, these concepts were born at a time when medicine had fallen into the extremes of organic orientation. Medicine had become a natural science based on the application of the principles of physics and chemistry to the living organism. The laboratory approach disclosed an incredible collection of more or less disconnected details and this inevitably led to a loss of perspective. The traditional etiologic view was a localistic one based essentially on Virchow's brilliant concept of cellular pathology. The symptoms of the disease were now explained by morphologic changes in the organs. Pasteur's and Koch's discovery of pathogenic micro-organisms made the infectious origin of the pathologic tissue changes the center of research. This one well defined mechanism soon became the model for all etiologic research. Other factors which had been discovered as causative agents, mechanical, thermic or chemical, followed similar principles.

The overpopularization of certain psychologic discoveries at the end of the nineteenth century had created a reaction against psychology and psychiatry by the medical profession. By way of the same reaction, it tended to become more somatologic. The reappearance of the term "psychosomatic medicine" and of the concept of the psychobiologic unity of the human being mark a renewed attempt to produce a synthesis of the total reactions of human personality. This process, started over a hundred years ago with less scientific equipment, had greater clinical intuition.

Few have understood the essence of this phase of medical development better than Gregg who wrote in 1936: "The totality that is the human being has been divided for study into parts and systems: one cannot decry the method but one is not obliged to remain satisfied with its results alone. What brings and keeps our several organs and numerous functions in harmony and federation? And what has medicine to say of the facile separation of the mind and body? What makes an individual what the name implies—not divided? The need for more knowledge here is of excruciating obviousness. But more than mere need, there is a foreshadowing of changes to come. Psychiatry is astir, neurophysiology is crescent, neurosurgery flourishes, and a star still hangs over the cradle of endocrinology. Contributions from the other fields are to seek from psychology, cultural anthropology, sociology, and philosophy as well as from chemistry, physics, and internal medicine to resolve the dichotomy of mind and body left us by Descartes."[6]

Since life itself is stronger than theories, the large number of sufferers who did not profit from the laboratory studies of scientists forced the medical profession by sheer

strength of numbers to re-evaluate the situation. The psychoneurotics who constitute probably the majority of all human sufferers wanted help. As a result one of the saddest anomalies of medical history developed. The physician whom these patients forced to listen to their psychologic complaints, who was unable to understand and to handle these symptoms with his one-sided training and equipment, began to dislike this type of neurotic patient. He refused to consider them as really sick and often accused them of malingering. In order to defend their scientific attitude, physicians had developed a distaste for psychologic facts and now they turned this distaste against their psychoneurotic patients. These patients were regarded as a nuisance and were considered a living accusation against the inadequacy of prevailing methods and dogmas. The physician became impatient with the nervous sufferer and stubbornly refused to deal with his symptoms on a psychologic level.

RÔLE OF MODERN PSYCHIATRY IN THE DEVELOPMENT OF MEDICINE

Psychiatry, as the study of the morbid personality, was to become the gateway for the introduction of the synthetic point of view into medicine. Advances in neurology paved the way for a more comprehensive understanding that in the last analysis all parts of the body, directly or indirectly, are connected with a central governing system and are under the control of this central organ. The central nervous system has both the function of the regulation of the internal vegetable processes of the organism and also the regulation of its external affairs, its relation to the environment. It is assumed that the complex neurophysiology of mood, instinct and intellect differs from other physiology in degree of complexity but not in quality. Whereas physiology approaches the functions of the central nervous system in terms of space and time, psychology approaches it in terms of those subjective phenomena which we call psychologic and they are the subjective reflections of physiologic processes.

Recently more and more evidence is emerging that probably the functions of the ductless glands ultimately are also subject to the functions of the highest centers of the brain, that is to say the psychic life.[7]

The fact that the mind rules over the body, no matter how much it was neglected by biology and medicine, is the most fundamental fact which we observe continuously during all our life. Our body carries out most complicated and refined motor activity under the influence of such psychologic phenomena as ideas and wishes. All our emotions are expressed by physiologic processes; sorrow by weeping, amusement by laughter, shame by blushing, fear by palpitation, anger by increased heart activity, elevation of blood pressure and a change in the carbohydrate metabolism, and despair by sighing. Because these psychomotor processes belong to our normal life and have no ill effects, medicine until very recently paid little attention to their finer investigations. These changes in the body as reactions to acute emotions are of a passing nature. When the emotion disappears, the corresponding physiologic changes also disappear. The study of neurotic patients showed that under influence of more permanent disturbances chronic dysfunctions of the body develop. At first these chronic bodily changes were observed in hysterics. Emotionally conditioned disturbances of the internal vegetative organs which are not under voluntary control, such as the heart and stomach, have also been observed.

This has led to the concept of "organ neurosis" later called "somatization reactions" following the second World War. These are disturbances of the internal vegetative organs caused by nerve impulses, the ultimate origin of which are emotional processes most probably localized in the cortical and subcortical centers of the brain. Another term often used for these disturbances is "functional disturbances" since the tissues do not show any morphologic changes discernible by the microscope. In

such cases the anatomic structure of the organs is unchanged; only the co-ordination and the intensity of the organ function is disturbed. They are reversible. Since these functional disturbances are caused by emotional factors, psychotherapy thus gained a legitimate entrance into medicine proper and could no longer be restricted exclusively to the field of psychiatry. Since these emotional conflicts arise during the life of the patient in his relationship with other human beings, the patient as a personality became an object of therapy.

Psychogenic factors in disease mean the production of physical symptoms by the powerful biologic urges which motivate our lives, fear, hate, love and the forces which drive men and women to heights of accomplishment and heroism but also to the depths of despair, to neurosis or psychosis, to murder or to suicide. These motivations can best be understood by studying their manifestations in thought, phantasy, dreams and behavior. Under certain conditions, particularly the intensification of these drives without adequate expression, they can affect the physiology sufficiently to produce symptoms in the psychologic, the muscular or the vegetative spheres.[8] More and more clinicians are beginning to suspect that functional disorders of long duration may lead slowly to genuine organic disorders based on visible anatomic changes. Thus the hyperactivity of the heart may lead to hypertrophy of the heart muscle; hysterical paralysis of a limb may lead, due to inactivity, to certain degenerative changes in the muscles.

This view of the causation of certain organic disorders means a remarkable change of traditional concepts. In these cases the pathologic-anatomic changes are secondary results of a disturbed function and the disturbed function itself is the result of chronic emotional conflicts. Thus, we have pathologic function as the cause of pathologic structure.

There is much evidence to show that just as the pathologic micro-organisms are specific and have a specific affinity to certain organs so also the emotional conflicts are different from each other and are liable in accordance with these differences to afflict different internal organs. Inhibited rage seems to have a specific relationship to the cardiovascular system; dependent, help-seeking tendencies seem to have a specific relationship to the function of nutrition. Again, a different and specific conflict between sexual wishes and dependent tendencies appears to have a specific influence upon respiratory processes.

The increasing knowledge of the relations of the emotions to normal and disturbed function requires that for the modern physician, emotional conflicts should become just as real and tangible issues as visible micro-organisms. Menninger emphasizes this point more dramatically by saying that this knowledge will bring an awareness of man's daily struggles as having as much or more to do with the way he may feel as bacteria or bullets.[9] He should be trained to use the psychologic microscope as he had been trained to use the optical microscope, a psychologic technic by which the emotional life of the patient can be subjected to detailed scrutiny.

This psychologic approach to the problems of life and disease brings the internal body processes into a synthetic unit with the individual's external relations to his social environment. It gives a scientific basis to such empirical everyday observations as that a patient often shows remarkable recovery if he is removed from his family environment,[10] or if he interrupts his everyday occupation, and thus is relieved from those emotional conflicts which arise from family life or professional activity. The detailed knowledge of the relation of emotional life and body processes extends the function of the physician. The physical and mental care of the patient can again be united in one hand. The division of the healing profession between organic and functional disease has been an artificial one based on insufficient knowledge of the functions of the body and personality in their mutual interrelation.[11]

PSYCHOSOMATIC INVESTIGATIONS

With the publication of the Journal of Psychosomatic Medicine in 1939[12] and the formation of the American Society for Research in Psychosomatic Problems in 1942,[13] research in this field, both clinical and experimental, was accelerated and extended in scope.[14] Various groups of investigators[15–20] working with animals were able to produce different types of psychosomatic responses. The physiologic expression of animals conditioned in such a way as to produce anxiety showed disturbances of gastrointestinal function in the form of diarrhea or constipation with a persistent loss of weight and an increased susceptibility to infection. More specific organ neurotic function may also occur such as pulse irregularities, pollakiuria, limping, incontinence, and premature ejaculation. Hudgins[21] was able to produce highly individualized configuration of visceral reactions in a group of people. His subjects were able to contract their pupils by a particular mode of thinking. This was brought about by a conditioning process.

The literature on the clinical investigation of psychosomatic problems has become voluminous. Since the physical reactions to emotional disturbances may take on any form, for the convenience of description one may classify and discuss these reactions under four headings (at the end of the war the American Army used seven categories):[22] (1) the gastrointestinal, (2) the cardiovascular, (3) the large group of aches and pains included in the category of headache, joint and muscle pains and (4) the allergies.

1. *Gastrointestinal.* Most clinicians are impressed with the emotional elements in peptic ulcer. Many[23–28] consider it to be a psychosomatic disorder. This approach makes understandable observations which previously were difficult to integrate into the accepted concepts of peptic ulcer. The scientific literature on digestive malfunctions and its relationship to emotions has been covered by the exhaustive works of Dunbar,[29] Alexander[30] and Schilder.[31]

Many workers[32–36] have noted recurrence of ulcer activity with the appearance of tension in the lives of ulcer patients. The character structure of the ulcer patient is such that when the proper stimulus presents itself he becomes embroiled in a conflict which produces tension. Alexander,[37] Mittleman and Wolff[38] and others have described the peptic ulcer conflict as developing from an unconscious longing for a dependent relationship and a reactive striving for assertive independence. Draper[39] describes his ulcer patients as forever striving to attain some goal notwithstanding difficulties which most men consider as insurmountable. By means of the electroencephalogram Rubin and Bowman,[40] taking the alpha index as a criterion of the passive personality, found a close relationship between peptic ulcer and a passive, receptive, fundamental personality structure.

Although the underlying conflict in the peptic ulcer patient appears to be the same, the outward appearance and attitudes vary considerably. Such differences depend upon the personality adjustments and defenses utilized and developed to solve interpersonal problems of which the ulcer conflict plays an important part. Thus the ulcer patient may appear to be talkative, taciturn, cheerful, sullen, belligerent, meek, cocky, bashful, misanthropic, amiable, hyperkinetic, sluggish, bright, dull, aggressive or unobstructive. It is therefore somewhat naive to believe that one can recognize the "ulcer type" by his appearance alone.[40]

In 1932 Cushing[23] postulated that operation on cerebellar tumors results in disturbed balance of the components of the autonomic nervous system supplying the esophagus, stomach and duodenum and that emotions might effect a similar imbalance likewise resulting in ulceration. Wolf and Wolff,[41] working on their subject Tom who had a gastric fistula, found during states of fear and depression a predominantly sympathetic stimulation resulting in gastric hyposecretion, hypomotility, mucosal pallor and decreased mucin production. Emotions of resentment, anger and anxiety

were found to be associated with hypersecretion of acid and pepsin, hypermotility, hyperemia and increased mucin elaboration, predominantly parasympathetic effects. When conflicts involving both fear and resentment existed, a dissociation response was observed frequently, resulting in hypersecretion of acid and pepsin and increased motility, but in this instance there was a *decrease* in mucin, a substance which ordinarily protects the mucosa from the erosive action of normal gastric juice. Such a conflict, then, results in physiologic changes that appear to be highly conducive to the development of erosion. Sustained emotional tension, productive of overstimulation of the stomach, can lead eventually to ulceration. Recurrent ulceration following subtotal gastrectomy may be explained partly by the conflict situation persisting or reappearing in the presence of sufficient remaining acid- and pepsin-bearing glandular tissue. Post-gastrectomy symptoms of weakness, tiredness, sweating, lassitude and procrastination form a not uncommon syndrome observed postoperatively in those patients whose conflicts have not been solved or who are unable to meet the problems of the moment adequately. This syndrome is seen most commonly in veterans.

Zane,[42] van der Heide[43] and Esterman[25] all conclude that peptic ulcer is a psychosomatic disease; that the causative factor which is operative in the vast majority of cases is the psyche mediated through the autonomic nervous system, thus engendering a morbid physiologic state conducive to the initiation, extension and chronicity of the lesion. This concept affords a better understanding of the many confusing manifestations of the ailment and makes available a more flexible and effective approach to them. As a gastro-enterologist, Sydney Portis believes there is need for a healthy cooperation in the pooling of somatic and psychologic knowledge; that then and only then will the patient get real service from the medical profession.[44]

Similar studies have been made on cases of non-specific ulcerative colitis and it has been shown that many of these patients have character traits which cause them to react to certain external situations in a similar way. The onset or recurrence of the disease is preceded by an emotional trauma which produces a specific internal conflict, an acute love loss combined with humiliation. This makes these patients feel their inferiority as men or women.[45–48]

The clinical syndrome of anorexia nervosa and its attendant complexities has also been the subject of considerable study.[49,50] Nearly all investigators emphasize the factor of the child-parent relationship, especially the relationship to the mother as the most important factor in the disease.[51] The importance of the interaction of the environment and the personality organization of the patient has been outlined by Waller, Kaufman and Deutsch.[52] This malady is characterized by depression of a wide range of functions: basal metabolic rate, temperature, estrogenic function, blood pressure, gastrointestinal muscular activity and its secretions. This psychosomatic disease behaves contrariwise in this respect to the other psychosomatic diseases in which there is exaggeration of one or more natural functions.[53]

2. *Cardiovascular.* There are indications that emotional conflicts of another kind may cause continued fluctuations of the blood pressure which overtax the vascular system. Psychosomatic research in this field is not intended to be definitive but merely serves as a basis for further systematic studies which may lead eventually to an etiologically founded therapeutic procedure. Alexander[54,55] came to the conclusion that the early fluctuating phase of essential hypertension is the manifestation of a psychoneurotic condition. This is based on excessive and inhibited hostile impulses. Extensive studies of the emotional lives of patients with hypertension have been published by Dunbar[56] and Wolfe.[57] They call attention to the increased tension and occasional spasm of voluntary or smooth

muscle, either or both of which may be alleviated as unconscious conflicts become conscious. They believe that this tension is part of the whole defense mechanism; psychologically and physiologically a general attitude of being on guard. Leon Saul[58] reports the finding of hostility in his series of cases. Katz and Leiter[59] state " . . . that numerous and various approaches to the problem of hypertension have been made and are still necessary to its solution. Not the least of these is the psychosomatic study of man in relation to his environment, internal and external alike." Morris,[60] in a study carried out on student nurses and student pilots, found no correlation between changes in the pulse and blood pressure and instability. Instability instead of hostility or repressed resentment were looked for which may account for his conclusions. Hamilton[61] investigated the psychophysiology of blood pressure in 373 young males with elevated blood pressure and found them as a group to tend toward less physical and social activity. They tended to move and walk more slowly and exhibited a definite tendency to avoid exercise and sports. They were somewhat less dominant and self-assertive. They had fewer friends and were somewhat more susceptible to anger. In a case of identical twin brothers, hypertension occurred in one and not in the other. The twins were of exactly opposite temperaments.[53]

Binger, Ackerman, Cohn, Schroeder and Steele, in a monograph on Personality in Arterial Hypertension,[62] came to the conclusion that "What appears to differentiate this from other neurotic disorders is the fact that after prolonged unresolved struggle between dependent strivings and compensatory aggressive drives, there is finally submission on the part of the patient to the hostility of the parent figure and acceptance of defeat of his own aggressive drives. When this occurs, anxiety, depression and temporary disorganization of the adaptive functions of the personality manifest themselves. Such acute emotional decompensations coincide with the discovery of hypertension. The failure of the integrative functions of personality, the inadequacy of the characteristic defenses against anxiety, the inefficiency of the repressive mechanisms and the inability to develop an organized neurosis, rather than the nature of the underlying 'instinctive' drives, are what appear to differentiate this disorder from other seemingly similar ones. Although there may be a relationship between the disorder of the personality described and hypertension, the conclusion has not been drawn that one is the 'cause' of the other."

Perhaps in no other system of the body is the iatrogenic factor as important as in the cardiovascular system. Functional disorders of the heart induced in the patient by the physician during his examination or by his manner of discussion of the patient's condition, occur more frequently than they should. Doubt in the patient's mind as to the integrity of the heart is a very frequent cause of chronic incapacity and a type of disability that is extremely difficult to alleviate in a neurotic patient.[63,64]

3. *Headaches, Joint and Muscle Pains.* Patients with chronic headache present a considerable problem to the practitioner both because of their numbers and because of the stubbornness with which their symptoms often persist despite every effort of treatment. The great majority of all patients with chronic headache fall into one of three groups, migrainous, post-traumatic or psychogenic.

The psychogenic headache may be produced experimentally[65] by the intravenous injection of a small amount of histamine, that is, by stimulating the pain-sensitive structures in or near the walls of the large intracranial arteries by forcible vasodilatation. There is no definite evidence at present that this headache is caused by histamine sensitivity or by any other disorder of histamine metabolism.

Regardless of the precise mechanism of the production of pain, there is abundant clinical experience to prove that all three types of headaches are readily precipitated and made worse by emotional stress and

inner conflicts. As in the other conditions mentioned before in this paper, neither the psychologic nor the physical aspect of the headache can be neglected with impunity.

Alvarez,[66] H. G. Wolff,[67] Moersch,[68] Weber,[69] Touraine and Draper,[70] Knopf,[71] Slight[72] and Trowbridge and his co-workers[73] all investigated the migrainous personality and found these patients to be intelligent, hypersensitive, tense, worrisome, easily and suddenly fatigued, sensitive to smells, drafts and bright lights. They are usually politely obstinate and somewhat paranoid. Donald Ross and Francis McNaughton,[74] in their objective studies in migraine by means of the Rorschach method, found in these patients a persistence toward success, difficulty in sexual adjustment, perfectionism, inflexibility, conventionality and intolerance. Some of these are obsessive-compulsive features and all have been found in migraine by clinical personality study.

Dunbar[75] was one of the first investigators to describe the personality profile of sufferers from rheumatic disease. She divides these patients into two separate groups, one group with recurrent polyarthritis but with little or no cardiac damage and the second group with heart disease but with a history of only vague "growing pains." Time does not permit going into this fully and the reader is referred to Dunbar's description.

This type of patient attempts to please irrespective of whether the person to be pleased is superior or equal, male or female. The conflict to which he is subject makes his need to please especially acute.

In Scotland, Halliday[76,77,78] found that patients with rheumatoid arthritis have an air of detachment and lack exteriorized tension. They show a quiet friendliness and a comparative absence of depression. In his opinion it remains to be seen whether further research will uncover a more specific rheumatoid personality type.

Toward this end, many workers[79–85] have contributed important observations on the relationship of psychologic mechanisms. Seeking an understanding of physiologic mechanisms, other investigators[86–88] studied the relationship between emotional reactions and skin temperatures in these arthritics. Johnson, Shapiro and Alexander[89] found that these patients express and discharge unconscious emotional tendencies through the voluntary muscles just as in hysterical conversion. They assume that these muscle spasms and increased muscle tonus may, under certain conditions, precipitate an arthritic attack. William Menninger[9] reports that in the late war there were many cases of psychogenic disorders characterized by joint or musculoskeletal pain resembling myositis or fibrositis.

The occurrence of neurotic manifestations in and around the spinal column has been rather neglected by most medical men. Jones and Lovett[90] have discussed the features of the neurotic back symptoms quite thoroughly. Whitman[91] distinguishes between the "neurotic spine" and the "hysterical spine." Wechsler[92] includes certain back symptoms as examples of conversion hysteria. He comments upon the fact that pain in the back may be a common and persistent neurotic complaint. Neuralgias and myalgias of the back as types of organ neurosis have been described by many investigators.[93–96] Saul[97] investigated the mechanism of psychogenic back pain and found that, like many other psychosomatic symptoms, it may result from an actual local physical condition which is exacerbated or possibly entirely caused by emotional tensions. Fetterman[98] advises that organic disease of the back be ruled out first because the symptoms in vertebral neurosis are no different from the complaints in organic disease. This self-evident statement applies to all types of functional disorders. However, the symptoms in the aggregate may give a clue to their psychic origin. Since psychogenic backaches are frequently organic at the outset, he describes clinical material often overlooked and gives certain points in differential diagnosis.

4. *Allergies.* The literature on psychogenic factors in asthma has been well summarized by Dunbar[29] and Wittkower.[99]

In 1937 the Asthma Research Council in their "Report of Progress" for that year state: "Dr. Strauss has continued his investigations of the psychogenic factor in asthma and has concluded that psychic factors contribute to the asthma syndrome in even greater measure than had been thought likely."[100] In their "Report of Progress" for the next year on vasomotor rhinitis they found "that the psychologic element was of even greater importance than they had anticipated."[101] Eyermann[102] reports that those interested in allergy pay too little attention to the psyche and that those interested in the psychic conditioning of bronchial asthma are not aware of the possible allergic explanations for the vagaries of this disease. Karnosh[103] points out that no allergic person can be adequately evaluated without considering the personality structure in which the disease is implanted. Mitchell, Curran and Myers[104] found that the group of patients with negative skin-reactions are also the multiple complaint group. They express a variety of illnesses and complaints indicating a strong content of factors characteristic of psychologic maladjustment. Of fifty unselected cases of bronchial asthma taken from the allergy clinic by Neil McDermott and Stanley Cobb,[105] 72 per cent seemed to have an emotional component in their asthmatic attacks.

In the monograph on Psychogenic Factors in Bronchial Asthma, Thomas Franch[106] attempts to define the particular type of conflict commonly found in asthmatics. In summarizing the literature and findings, he states: "the impression gained is that attacks of bronchial asthma seem to be associated with very considerable variety of emotional conflicts. Outstanding among these are the suppression of any sort of intense emotion, threats to dependent relationships and to the security based upon them, and sexual conflicts. The outstanding personality traits of asthmatic children seem to be over-anxiety, lack of self-confidence and a clinging dependence on the parents which appears to be a reaction to a tendency to over-solicitude upon the part of the parents." Using the Rorschach test and psychiatric examination, Viva Schatia[107] found asthmatics to have compulsive personalities without evidence of phobias or obsessions.

If the majority of asthmatics suffer from unsolved conflicts, it is a matter of interest then to find out the proportion of asthmatics among those who have supposedly "solved" their conflicts through a flight into psychosis. Leavitt,[108] investigating almost 12,000 patients suffering from functional psychosis in State Hospitals, found only ten cases of asthma. This is only about one-twentieth of the number of asthmatics found in the general population.[109] MacInnis[110] in a survey of two mental hospitals each having 3,500 patients found only five cases of bronchial asthma in five years in one hospital and none was present in the other.

In the case of urticaria the rôle of psychologic factors has long been recognized. The literature on this subject has been reviewed by Dunbar,[3] Fenichel,[111] and Sutton and Sutton.[112] Fenichel indicated that the tendency of the skin to be influenced by vasomotor reactions, which in turn are evoked by unconscious impulses, has to be understood from the point of view of the general physiologic functions of the skin. It displays four characteristics whereby it represents a boundary between the organism and the external world. (1) In its protective function, the skin treats internal like external stimuli and uses vasomotor functions as an armour. (2) The skin is an important erogenous zone. In addition to the stimuli of touch and temperature pain, too, may be the source of erogenous cutaneous pleasures. (3) Being visible, the skin is a site for expressions of conflicts around exhibitionism. These conflicts concern not only fear and shame but also various narcissistic needs for reassurance. (4) Anxiety is physiologically a sympathicotonic state, and sympathicotonic reactions of vessels in the skin may represent anxiety. It is well recognized that the skin may react to normal emotional situations by flushing, pallor or sweating, and that the degree of

this reaction depends upon the individual. Davis and Bick[113] suggest that in the same manner anxiety is a quantitative exaggeration of a mild tension of nervousness. Therefore, some forms of dermatitis are quantitative exaggerations of mild skin reactions. This is an additional symptom of an anxiety state occurring in a sensitive individual whose anxiety is reflected through the skin rather than through the gastrointestinal tract or cardiovascular system.

People can be just as sensitive to certain ideas or situations as others to pollens. Menninger and Kemp[114] report a case of urticaria in a young man caused by his inability to "be a man" in a love affair. Saul and Bernstein[115] suggest the possibility of a relationship between certain states of allergic sensitivity and states of intense frustrated longing. There are certain differences between acute and chronic urticaria. Chief of these is the fact that while specific allergens are usually found to cause acute urticarias, it is exceptional to find this etiology in chronic cases. In the latter there are a great variety of factors operative, among them the psychologic and endocrinological.[116] Kaywin[117] came to the conclusion that his patients with chronic urticarias were shy, easily embarrassed, prone to blushing, relative passive-dependent and immature, with, perhaps, a tendency toward exhibitionism.

As a dermatologist and allergist, Sulzberger is skeptical of the psychologic factor. He states: "Psychic and emotional influences can perhaps elicit urticarial attacks and in many ways perhaps even favor the creation of allergic states and the elicitation of allergic reactions. I have never had the opportunity to observe purely psychogenic urticarial attacks, but their existence is reported by many careful observers such as J. Jadassohn, Sack and others in Europe and, in America, Stokes, Pillsbury, Kulchar and co-workers, in articles which merit careful reading by all interested in the problems of psychogenic and emotional effects in various dermatoses."[118]

Thus, in reviewing these four arbitrary groups of psychosomatic problems, only a rabid psychosomaticist would insist that the impact of a persistent emotional situation upon a certain temperament is the whole story in the creation of such diseases. Obviously, there must be other mechanisms that we are as yet unaware of; physical, endocrine, humoral, etc. We must also consider that psychosomatic diseases possess a long life cycle and that the incubation period may be of many years' duration. Unfortunately our methods of approach are still crude and the interrelation between the autonomic, the somatic nervous system and the endocrine organisms are so close and so complex that it is difficult to isolate the reactions between the various systems.

It becomes apparent that it is not only the variety of emotion which is important but the way in which these emotions are experienced. One individual trembles, the second vomits, the third gets palpitation, the fourth gets increased peristalsis, the fifth flushes, the sixth pants for breath, the seventh feels a lump in his stomach; and these symptoms are reflected in physical expressions such as changes in blood pressure, increase or suppression in gastric secretion, increase in blood sugar, increase in intestinal secretion and tachycardia.

The diagnosis of these diseases depends upon a perspective of the composite picture in which a study of the personality and life history of the individual is a vital consideration. The life history should include a panoramic survey of the patient's life, his reactions to members of his family, his social and economic status, his loves, his fears, his strivings and his hates in a tridimensional history. The psyche and the soma of the patient should be viewed stereoscopically.

In this development of a psychosomatic disease there are five phases: (1) The constitution of the patient; (2) the exaggeration of a normal function; (3) the lability of the exaggerated function; (4) the fixation of this exaggerated function and (5) somatic changes.

It is in the transition between the fixation stage and the somatic changes, that is, the

eludication of the mechanisms whereby fixed exaggerated function results in organic changes that one of the main problems in psychosomatic medicine lies. Usually by the time the somatic changes are crystallized the personality changes are also crystallized.

Psychotherapy to be effective must take place in the first three phases. It is of less avail in the fixed and especially in the somatic phase. In the last two phases, surgery has done much to reduce the exaggerated function to a lower level (sympathectomy, vagotomy, gastrectomy and thyroidectomy). However, in such fixed psychosomatic disease psychotherapy begins when the operation is finished.[53]

TEACHING PSYCHOSOMATIC MEDICINE

Whether psychosomatic medicine, in its revival as an attempt to integrate psychopathology with heretofore isolationist biology and physiology, is to be considered a new specialty or a new form of medicine is a question that only the future can decide. At the present time there are two somewhat incompatible connotations of the term. In the opinion of the American Society for the Study of Psychosomatic Problems (soon to be called The American Psychosomatic Society) psychosomatic medicine refers only to a point of view. This is a psychologic orientation to all disease. In this concept it is a guiding principle of medicine which should apply to all illnesses and should represent the view of the surgeon and internist as well as that of the psychiatrist.[12] From this point of view the term "psychosomatic medicine" is a punitive one intended to reorientate medical thought from localistic thinking. If in years to come this orientation is accomplished, no doubt the term itself will be dropped as physicians learn to use this approach naturally.

There are others such as Halliday[78] for whom the term "psychosomatic medicine" is used to describe certain diseases. In his opinion the concept of a psychosomatic affection in its developed form brings into relationship a large number of seemingly unrelated facts. The outlook gained shows that many "localized diseases," the names of which have been found scattered throughout textbooks of medicine under the headings of the various anatomic systems, may now be grouped under a unifying etiologic category. The term psychosomatic affection is therefore a valid symbol which provides a new instrument for thinking, for investigation and for the direction of action. In his opinion the psychosomatic affections comprise many of the chronic recurring forms of sickness and they incapacitate rather than kill.

These two divergent concepts serve to reflect the many confusions inherent in the change of traditional concepts of disease. Those interested in psychosomatic medicine today are thinking in terms of the necessity for the organism to maintain a homeostatic equilibrium within itself and within its environment. In the science and the practice of medicine there is a need for a new approach to classification based on psychosomatic concepts. Here the major contributions have come from physiologists on the one hand and from medical psychologists on the other. But it has been difficult to bridge the gulf between these two disciplines. Existing nosology is inadequate in both psychiatric and somatic aspects. The disease entities now recognized in each of these fields have little relevance to the organism as a whole or to the "organism-environment continuum." These are essential concepts in the psychosomatic approach. Psychosomatic disorders are not entities that can be catalogued under the earlier diagnostic labels invented by psychiatry or internal medicine or a combination of the two.

What is needed is a system of classification which will aim not at defining disease entities in the traditional sense but rather at describing dynamic processes in ill persons. It should begin with the organism-environment continuum, and its material should relate to the flow of energy in a field of tension. Illness in the biologic sense represents a failure of the organism's adaptability. The availability and lability

of the defensive mechanisms are of the utmost importance in influencing the clinical course and the therapeutic possibilities. To verbalize these conditions requires new medical nosology and the aid of general semantics.

In the present state of knowledge methods are not yet available to test the question of causation in the dynamic relationship of "psyche" and "soma." In Dunbar's opinion we are seriously in need of more clinical studies to trace the sequence of events in both spheres and of more experimental studies relative to the physiologic and psychologic components to clarify the problems of pathogenesis. The causality in disease constitutes a chain of circumstances and events and is never a simple and isolated factor.

In view of these difficulties it is not surprising that even with the present-day knowledge of psychosomatic medicine there is still far too wide a gap between the use of the word psychosomatic (and sometimes its glib use) and the deep understanding of what it really means and its therapeutic implications. What has been gained, however, is the acceptance of the psychosomatic approach by the medical profession though there are still many who are not even receptive to the ideas underlying this concept. Psychosomatic medicine no longer needs an apology.[119,120] It has passed that stage. One may consider this acceptance as the first phase of the problem. The second phase, upon which we are now entering, consists of the task of teaching this new discipline to students and to those physicians who are interested in reorientating themselves to medicine. The study of psychosomatic medicine is largely in the hands of the youth of our profession.

As mentioned at the outset, this is a major task of education and we must look to the universities to meet the problem. In the meanwhile there are many graduates interested in learning this point of view and the literature in clinical journals aims to satisfy this need.[121–131] That they do not satisfy this need fully is due in part to the fact that not enough physicians are trained in the basic sciences of this new approach. Just as one would not expect to make an adequate medical diagnosis without first having been trained in anatomy, physiology, chemistry, pathology, medicine, etc., so one can hardly expect the physician to understand the psychosomatic approach without first learning the broad patterns of human motivation and personality development, its adaptations and its maladaptations. He must be able to recognize anxiety in its many forms of expression and he must be as familiar with the neuroses as he is with bacteria. Without this knowledge his study and reading of psychosomatic literature cannot but be confusing.

In the writer's opinion it is very difficult if at all possible to teach the psychosomatic approach to those whose "orthodox" training and orientation has become "fixed." To them, physicians who seem to have gained some insight into psychologic phenomena are either disregarded on the whole or relegated to the group of more or less queer doctors who have wandered off into philosophy. In attempting to teach the psychosomatic approach in the early nineteen thirties, the writer found himself in the unfortunate position of being considered an internist by the psychiatrists and a psychiatrist by the internists.

On the other hand, medical and premedical students absorb these teachings with avidity. Theoretically, the average student knows that there is a relationship between the soma and the psyche, but actually he has relatively little conviction of the reality of this relationship. Following a series of lectures on psychosomatic problems given by the writer over a period of years to the McGill Psychological, Premedical and Medical Undergraduate Societies, a group of senior medical students, resident physicians and young practicing physicians was formed to study the subject of psychosomatic medicine. Classes were started in the writer's office and met twice weekly. These sessions lasted from three to four hours each and extended through the

winter seasons. By 1938 the class consisted of fifteen members.

In the beginning the instruction was very informal, haphazard and left much to be desired. At this stage the lack of organization was made up for by the enthusiasm of the group. Later, however, the course took on a more systematized and graded form. At the outset the patient-physician relationship was discussed. Physicians have two kinds of relationships with their patients. The first, and the one best understood, is the reality relationship. The second is a symbolic one in which the physician plays a psychologic rôle which is not altogether determined by reality. Here the emotional attitudes of the patient are based on earlier experiences. He may identify the physician with earlier figures such as the father or mother who have played an important rôle in the early life of the patient. This may produce a positive or negative transference.[135] The physician must be aware of it for a great deal of his success in therapy will depend upon the way he handles these attitudes. The physician on his own part may also develop certain emotional reactions toward the patient, countertransference and hostility are not infrequent and must be avoided if possible. The therapeutic values inherent in the patient-physician relationship are considerable and should be developed fully.[132,133,134]

The next step was to study the normal development of the personality.[134] One of the most important attitudes in infancy and childhood is dependence. This dependency for food, shelter and protection is easily seen but the emotional aspects of this situation are much more subtle. The interrelationship of these two sets of factors, the practical things the child needs for survival and the emotional constellations centered around his biologic needs are crucial in the development of his personality. How these emotional needs are satisfied or denied predicates certain types of behavior upon which later neurotic symptomatology is based.

At first the infant's dependency manifests itself in a somatic way through the gastrointestinal tract (oral and anal needs). When these needs are not met adequately, thumb-sucking or constipation may result. As the child becomes older the zones of intense interest shift. By three and one-half to four years of age the genital and urinary zones become the foci of interest not only in himself but in those about him, usually his father and mother. It is a period of intense activity and he learns to give up his socially unacceptable impulses by the age of five. This is the period of "thou-shalt-not" and the child begins to identify himself with the person who is advancing the "thou-shalt-nots." This is the age of nightmares, mild phobias and inner turmoil. By six he is ready to meet the world in terms of ideas instead of soma; he is ready to be taught. There is a decline in the child's emotional activity and the beginning formulation of conscience.

All these childhood dependency relationships are reactivated when a patient becomes ill and accounts for the childish dependency some patients have for their doctors—the basis of the doctor-patient relationship.

At this stage of instruction the technical terms of "id," "ego" and "super-ego" were explored and correlated with the child's development.[135] During the "latency period" from about six to twelve there is a tendency for strong identifications with important people in his milieu. He resolves this identification after puberty by denying and rejecting everything there is about the person previously identified with. He is unwilling to be passive any longer and now identifies himself with and wants to be like all the other boys in his group. This is a period of intense attachment to his friends. Sexual development in all its complexities in regard to his training now takes place and the period of anxiety, tension, guilt, moodiness, insomnia and anorexia are observed.[137] These neurotic symptoms during adolescence may be considered normal though ten years later these same symptoms would have the significance of a malignant psychologic process. There is a continuous

conflict between powerful forces in the individual, perhaps never so powerful as during puberty, for the pleasure-seeking self is eternal and relentless. This is the time he identifies himself with the coach of the sport he is interested in. If his repressions are strong, he may turn toward the religious side and identify himself with the priest or minister, the Y.M.C.A. leader or some other group leader. This helps him weather the storms of puberty. It is at this time that he is capable of great esthetic and idealistic striving. It is at this period that he makes great plans for the future. The end of adolescence differs with each individual. Some become mature early in life while others never give up some of their adolescent attitudes and activities.[136]

The boy who comes through this adolescent period successfully settles down and feels reasonably certain of his ability to handle himself, his environment and his destiny. He leaves behind him his dependency on others and tries to remove his identification with figures of authority who dominated him in the past. It requires no great imagination to visualize the effects of important forces and counterforces which occur during this period of life and the damage they may do to the growing personality. This damage results in psychopathology.

The next object of study was the response of the individual to anxiety.[138] Each person handles anxiety in a different way. Many illnesses represent his way of dealing with it, his defense against the discomfort of anxiety or his translation of anxiety into a different area. When anxiety is expressed directly, he experiences it with all the physiologic and somatic discomfort implied in a sense of impending disaster. It is expressed through the cardiovascular apparatus in terms of palpitation, irregularities of rhythm, precordial discomfort, dyspnea and a sense of choking in the throat. If these somatic symptoms occur suddenly, as in an accident, the cause and effect are so obvious that the individual accepts these discomforts as a natural result of the experience. But should this anxiety be chronic and prolonged, he might interpret them in his own mind as the result of some organic disease of his heart or stomach.

Not all individuals, however, handle anxiety directly. He may "blot" out the anxiety experience from conscious recognition and develop a substitute for it, such as hysterical reactions. Or he may mediate this anxiety directly through organs and somatic functions, as in psychosomatic disturbances. In these cases the anxiety is mediated through the autonomic nervous system and is translated into functional disorders of various organs or parts. The fluctuations in severity of the symptoms at first run parallel with the fluctuations of anxiety. Later these dysfunctions may become irreversible. Or, anxiety may become focused on certain experiences such as fear of high places, closed places, animals, dirt, insanity, syphilis, pregnancy or cancer. Then again, anxiety may be thinly disguised and lead to obsessive thinking or compulsive activities, or it may be disowned and projected into others in terms of suspicion and distrust. When anxiety is expressed indirectly, the anxiety itself is never recognized by the patient as such, only the symptom formation. The sources of his anxiety are unconscious. It is of importance to note here that similar psychosomatic responses may result from fear, anger and resentment; and in the same way these emotions may remain unconscious and only the direct symptoms may make themselves known.

Just as medical students are taught the technic of blood counts, sedimentation rates, urine analysis, blood sugars, etc., so must the student of psychosomatic medicine learn various psychologic tests[139] which help to evaluate the intelligence and the dynamic forces at work in the production of symptoms. The class was instructed in the use of the following tests:

1. Word Association Test[140–144]
2. Thematic Apperception Test[145–152]
3. The Wechsler-Bellevue Intelligence Scale[139,153]
4. The Minnesota Multiphasic Personality Inventory Test[154]

5. The Picture Analysis Test[155]

Just as complicated and specialized medical tests (such as hormone assays or x-ray examinations) are referred to specialists, so must some psychologic tests be left for those specially trained. Thus the important Rorschach Test[156] was described briefly and an outline for its uses given so that it could be requisitioned when necessary. Just as the urine and stool excreta are examined to evaluate bodily functions, so are the mental excreta, the dreams, examined to evaluate emotional drives. While it is inadvisable for the physician inexperienced in the study of dreams to interpret them to the patient, still, with a little interest and study he can often glean, simply from the topics of the dreams, what is central in the patient's mind: hostility, anxiety, desires for ease or escape, the pressure toward work and accomplishment, needs for superiority, etc.

Up to this time instruction was purely theoretic.[157] It now became necessary to demonstrate clinical material. As a first step, the cases seen in the writer's office that day were discussed much as ordinary case reports are reviewed at clinical conferences, with this exception: The class was asked to try to obtain more information from the instructor than was given them in the case report itself.[45] The main complaints and a very short history and physical examination were reported and they were asked how to proceed from there on; what important direction of probing was suggested by the type of history given and what form of therapy was to be instituted. As soon as the class showed a true grasp of the general nature of the psychosomatic problems dealt with in every day practice, live clinical material was presented.

Since the classes were held in the evening, clinic and ward patients were unavailable for teaching purposes. Because of this and because it had many advantages, hypnosis was used to produce manageable models of almost all types of psychosomatic problems.[158–165] Hypnosis is one of the few experimental technics applicable to human beings whereby it is possible to produce major changes in the organization of behavior. Without discomfort or danger to the subject,[166] extensive alteration in the pattern of experience which constitutes the self, and in those controls of behavior which we know as volition, are altered. It is possible to produce artificially and temporarily the diverse symptoms of hysteria[167] or with equal ease to make a manageable model of compulsive or obsessive neurosis.[168] By the same means artificial "complexes"[169] are induced and made effectively subconscious. The class was then able to observe, under controlled conditions, with known antecedents, the eruption of unconscious strivings into the normal stream of behavior and the methods of defense set up against them. Anxiety, rage, fear, frustration and other emotions and situations were suggested to the subject and made subconscious by suggestion. The resulting somatic manifestations were observed and studied. These phenomena became a reality and the constant interplay between psyche and soma was observable from moment to moment.

While in actual patients some of the conditions demonstrated would take many years to develop, in this type of demonstration technic the whole "life cycle" was carried out in the space of an hour or so. In order to integrate these observations into the student's general training the somatic manifestations in these demonstrations were measured and visualized by means of the sphygmomanometer, respiratory tracings using the basal metabolism machine,[186,187,188] fluoroscopy of the stomach, heart and lungs, electrocardiograms, etc. For brevity, these hypnotic phenomena are listed below under general headings.[164]

1. Altered Visual Behavior[170]
   - (a) Decrease in visual acuity with blurring of vision
   - (b) Contraction of the visual field
   - (c) Difficulty in focusing gaze
   - (d) Decreased ability in depth and distance perception
   - (e) Subjective sense of color vision

2. Altered Auditory Behavior[171,172]
   (a) Decrease in acuity
   (b) Inaccuracy in localizing sound
   (c) Distortion of perception of sound qualities
3. Altered Motor Behavior[173,174,175]
   (a) General muscular incoordination
   (b) Specific motor disturbances such as paresis and paralysis, apraxias, speech disturbances, dysmetria, ocular fixation, pupillary dilation and nystagmoid movements
4. Other Types of Altered Behaviour
   (a) Analgesias and anesthesia[176–179]
   (b) Subjective reactions of nausea and vertigo[165]
   (c) Anxiety states and phobic reactions with their various physiologic concomitants[168]
   (d) Amnesias[180]
   (e) Revival of forgotten patterns of behavior[181]

At this stage of instruction all members of the class were taught the technic of hypnosis[182–185] and the indications for its use. The history of hypnosis in medicine was reviewed and the subject matter placed in its true frame of reference. The "thumbnail" description of the history of hypnosis by White of Harvard University is worth repeating here.[189] "Hypnotism was branded with the scarlet letter by a commission of scientists who dismissed Mesmer's findings on the ground that the phenomena, though real, were the result of imagination, hence not of the physical stuff with which science could safely deal with at that time. Ejected from the better consulting rooms, hypnosis was destined to wander for a hundred years in the slums of medical practice, from which disgrace she was not rescued until the eminent neurologist, Charcot, picked her out of the gutter, examined her reflexes, and pronounced her worthy of a place in medical research. More recently, through similar good offices by Hull of Yale University, she has been allowed to enter the portals of experimental psychology, where in the past twenty years she has begun to live down her reputation, learn the manners of the laboratory, and speak the language of polite science. Yet so recent is her social ascent that even in contemporary studies of hypnotism, there occasionally seems to linger the atmosphere of magic and darkened rooms rather than the clear light of reason."

Narcoanalysis and narcosynthesis, used during the war and since, is only a long recognized atypical form of hypnosis.[190,191,192] Instead of the term "hypnotism" the use of such terms as hypnoanalysis, hypnotherapy and hypnosynthesis has aided the acceptance of hypnosis by the medical profession.[183,193,194,195] It is now being taught in many of the best medical schools as a prerequisite subject in the post-graduate course in psychiatry.

The last topic for discussion in the course was psychotherapy.[122,196,197,198] This represents one of the chief interests of the student and physician. The limitations of psychotherapy as well as its possibilities were constantly kept in mind. Emphasis was placed upon the avoidance of two attitudes commonly observed in relation to this problem, a more or less complete rejection of, or a too enthusiastic acceptance of the "psychologic" in medicine. The wisest psychology will never replace penicillin or the need for an appendectomy. The various forms of psychotherapy were evaluated. The rôle of reassurance, supportive therapy and other anxiety-allaying technics were discussed. The differences in aim between these therapies and the so-called "anxiety-provoking" or "uncovering" psychotherapies were discussed in some detail. Insulin and electroconvulsive therapies,[199] adrenalin desensitization,[200] narcoanalysis, narcosynthesis and hypnotherapy were reviewed. An attempt was made to help them recognize the more malignant emotional conditions so that they might be referred to specialists in that field. The use of empathy instead of sympathy in therapy was stressed. It was also emphasized that some psychoneurotic patients can never be completely well and that they must return from time to time to the physician for support and

guidance much as the diabetic and pernicious anemia patients remain under the supervision of the internist.

During the early part of the course members of the class became aware of the considerable tension with which some of their prejudices were charged. It was difficult at first for them to see the emotional and organic elements in illness stereoscopically. There is still a trace of the dichotomy of mind and body in the use of the term "psychosomatic" and the student is apt to separate instead of integrate the components of the disease. The ability to see illness as a dynamic, constantly changing adaptation to the stresses and strains, internal and external, to which the patient is exposed requires considerable effort and training. Obviously, this type of training should begin in the preclinical years.

To see what could be done for the general practitioner, an experimental graduate course was given in 1946 to twenty-five general practitioners of all ages to determine whether these men can be taught to practice in their offices the kind of medicine psychoneurotic patients need. This course was sponsored jointly by the Commonwealth Fund and the Division of Postgraduate Education of the University of Minnesota.[134,201,202] Two weeks were considered adequate without depriving the busy physician of too much of his time. The teaching staff was drawn from the ranks of younger psychiatrists and somewhat older internists. Instruction was both didactic and clinical. Careful analysis by both students and instructors at the end of the course furnished evidence that this type of graduate education had been valuable in a practical sense.

A discussion on "The necessity for reorientation in medical education from the psychosomatic point of view" held in the summer of 1947 under the auspices of the American Society for Research in Psychosomatic Problems, revealed how complex and difficult this undertaking is at the present time. Many leaders in medical education took part in this discussion and it was believed by several that such a reorientation must await the time when those who guide the medical faculties see for themselves the need for this type of training.

At the present time there is much to be said for the suggestion made by the Canadian Association of Medical Students[203] and approved of in principle by the Editors of the *Canadian Medical Association Journal*[204] for apprenticeship to a physician as a method of teaching. This holds true especially in the field of psychosomatic medicine where clinical training is essential.

SUMMARY

The need for a psychosomatic approach to the problems of medicine has been recognized for more than two thousand years. The reasons for the lack of progress in this field are given. The recent growing interest and research in psychosomatic medicine has resulted from the realization that many illnesses treated by the physician cannot be understood from an organic point of view alone. The steps by which psychiatry has become integrated into medicine itself are delineated. Research work done on psychosomatic problems is reviewed. The results of this research have led to the acceptance by the medical profession of the psychosomatic attitude, namely, not to study the soma less but to study the psyche more.

To make the medical profession aware of the need for a psychosomatic attitude toward medical problems may be considered to be the first phase of the question. The second phase, upon which we are now embarking, consists of the task of teaching this subject to medical students and to those physicians who have graduated since the advent of the last war.

A brief outline of the writer's method of teaching psychosomatic medicine since 1936 is presented.

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Seminars on Protein Hydrolysates

Assessment of Knowledge Concerning the Clinical Use of Protein Hydrolysates and Pure Amino Acid Mixtures*

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IN this series of seminars† the primary intention has been to evaluate the use of protein hydrolysates for clinical purposes. It is convenient to comment on the fresh light they shed on (1) the physiology and pathology of protein metabolism and (2) the therapeutic and nutritional advantages of protein hydrolysates and other amino acid mixtures.

PHYSIOLOGY AND PATHOLOGY OF PROTEIN METABOLISM

Peters opens the series with an able and concise survey of the effect of injury and disease on nitrogen metabolism, first indicating the factors which influence the amount of nitrogen stored or retained in the body at any one time and then discussing the effects of protein restriction, starvation and work. He has wisely stressed that the optimum proportions of the amino acids for growth and maintenance have been only roughly ascertained. Like the growing animal the protein-depleted animal can apparently use a great deal of dietary protein.

It is important to note that although a sustained positive nitrogen balance is accepted as proof of previous protein depletion, failure to establish a positive balance certainly does not exclude antecedent protein depletion. This failure may be due to insufficient energy or to a protein intake deficient in quantity and quality. Dissociation in time of feeding of one essential amino acid from its fellows will prevent optimal use being made of the whole mixture.[1] Failure to achieve a positive balance may also be due to the catabolic response to injury, e.g., acute haemorrhage, operations and injuries, or to what has been called the 'toxic destruction of protein' associated with acute febrile illnesses.

Peters traces clearly the lack of success in preventing such losses of body nitrogen in the acute catabolic phase after trauma even when diets are administered which should be adequate in protein and far in excess of the energy needs of the patients. Peters finds that the amount of protein destroyed seems to vary with the severity of the injury or disease if the term 'severity' is loosely defined. This is in agreement with the present writer's experience.[2]

There is now a mass of evidence that a negative nitrogen balance of considerable degree almost always follows major accidental injuries although curiously the nitrogen loss after osteotomies is much less than after accidental fracture of the same bones, and a nitrogen balance can be made positive without difficulty after the repair of inguinal hernias but not so readily after appendicectomies.

Peters notes that the continued negative nitrogen balance after an acute illness often continues despite high protein diets and persists even after the temperature is normal

† These seminars may be found at the end of the references on page 890.

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and symptoms and signs of the illness have disappeared. In this case the losses of nitrogen seem to be related to the inherent gravity of the disease and not to its clinical manifestations. As the present writer[3] pointed out the degree of fever following injury—traumatic fever—is so slight that we cannot hold fever responsible for the marked wastage of protein which may occur after an injury such as a fracture. Further, disuse atrophy is not the major cause of the loss that follows injury.[3,4]

Strangely enough none of the papers refers to the remarkable parallelism in the behaviour of sulphur and nitrogen during the increased protein catabolism after serious trauma. The present writer drew attention to this many years ago.[6] Incidentally, in the light shed by the brilliant work of Schoenheimer and his colleagues in which it was shown that the distinct streams of exogenous and endogenous streams of metabolism postulated by Folin were in reality inextricably mixed, it is sometimes forgotten that it was the catabolic reaction to injury which demonstrated that urea was as much a product of endogenous metabolism under these circumstances as was creatinine.

Munro and Cuthbertson[7] showed that there is no increased loss of nitrogen after fracture of the long bone of a rat depleted of protein by being fed for some time on a protein-free diet. Evidence from the human field bears this out and indicates that protein is used in this profligate manner after injury only by previously healthy persons, and that after the height of the catabolic phase the loss of nitrogen gradually diminishes and, if an adequate diet is supplied, a positive nitrogen balance can be attained.

Just as Shaffer and Coleman[8] were unable to prevent a negative nitrogen balance during the early stages of typhoid fever, although able to mitigate the loss by increased intake of energy, so the writer[9] was also generally unable to attain nitrogen balance at the height of the catabolic phase following a severe injury. In this connection it is of interest that Browne and his associates[10] found that during the period of positive nitrogen balance which succeeds the negative or catabolic phase renewed injury causes little waste of nitrogen.

Peters points out that attempts to prevent nitrogen loss in the early days of a fever, such as typhoid, were carried through with diets containing quantities of protein which, although considered high in those days, are not by present standards really so very high. Anorexia was the factor which prevented large quantities being ingested. The problem of feeding such patients has been reopened by the development of intravenous forms of alimentation. But despite all modern aids Grossman et al.,[11] Howard et al.[12,13] and Browne et al.[10] were unable to establish nitrogen equilibrium even with large amounts of protein diets high in energy value in patients with severe, acute infections or after serious injuries or operations.

The significance of positive results achieved by some tends to break down when the cases are studied in detail. The apparent success of Mulholland, Co Tui et al.[14] in achieving a positive nitrogen balance in patients with gastrectomy by means of protein hydrolysates may have been due to the fact that these operations were performed chiefly on chronically wasted patients. Studies of persons with large exudative lesions, e.g., burns, must also be rejected for balance purposes unless the quantities of nitrogen lost in the exudates have been measured.

Peters suggests that the increase in nitrogen loss may be more apparent than real as it may be related to the protein intake only which is minimal immediately after an operation or severe injury. This is not in accord with the present writer's experience with fractures although he would agree with the view that injury appears to provoke no malicious destruction of protein but acts simply to compel the expenditure of a certain amount of tissue protein. Upon many occasions the writer has pointed out his belief that this catabolism of protein is part of a primitive reflex related to the need for energy and new materials by the injured animal which cannot search for its food.

The strange thing is that even when food is available during this period, the organism appears to make little use of it being, in general, geared to a catabolic or at least anti-anabolic phase. During this period an increase in energy intake does mitigate the loss to some extent. Elsewhere reference has been made by the writer[2] to the fact that anabolic activity may be going on but that this is masked by a more general catabolic effect. It is debatable if the administration of extremely large quantities of protein and a diet high in calories can spare native protein and it may be unwise to try to correct it. Indeed, there may be no special advantage in trying to correct this primitive catabolic reflex for, as Peters points out, Hirschfeld et al.[15] found that the early administration of large amounts of protein to burned patients provoked diarrhoea and other untoward symptoms. In any case, previously healthy patients are soon able to take large quantities of food and thereby protect and restore their tissue losses.

One cannot really go much further than agree with Peters' statement that there is an impression that high protein diets improve the sense of well being and hasten the appearance of the anabolic phase, and that the patient who incurs an acute injury while in a state of debilitation deserves a high protein and energy rich diet from the start because he can use protein efficiently.

It should be noted that the work of Croft and R. A. Peters[16] on the nitrogen-saving effect of methionine in burned rats, which is referred to by J. P. Peters, has not been confirmed by the senior of these two workers and his later colleagues.[17] Further, Sellers and Best[18] substantiate this lack of a nitrogen-saving effect with rats fed reasonable amounts of methionine in their basic ration.

So far no one has been able to supply any satisfying evidence that the catabolism of protein is actually caused by a requirement for any specific amino acid although after a burn one would anticipate a higher requirement of sulphur-containing amino acids to make good the loss of sulphur by way of the skin than after a fleshy wound. As the writer[6] has pointed out the partition of nitrogen and sulphur in the urine during the early days following injury is similar to that associated with the ingestion of protein in normal quantities.

Allison in his seminar discusses the nature of the protein which can be mobilized or catabolized during periods of protein or energy insufficiency. When these stores are reduced in malnutrition or disease, the body loses the capacity to repair damage, to build antibodies and to maintain the mechanisms which create barriers to destructive forces. This is a question of degree for it is only when depletion is carried beyond a certain extent that, for example, we find evidence of a failure to build antibodies. Recent work at the Rowett Research Institute indicates that the matter cannot be stated as simply as Allison makes out. Similarly, his statement that regeneration of destroyed tissues takes place only in the presence of sufficient nitrogen to create a positive nitrogen balance is an obvious overstatement.

Allison quite rightly points out that we have no evidence that there are any reserves of essential amino acids which can be drawn upon to supplement an inadequate diet without breaking down body proteins. He considers that the labile cytoplasmic proteins of the tissues—the protein stores—are different in character in the depleted state than in the normal which is presumably meant to mean that there is a quantitative rather than a qualitative difference. How far this is based on Roche's[19,20] work is not clear, but her work so far has not been substantiated by further experimentation.

The reservoir of body protein is thus distributed in the tissues which with different capabilities supply nitrogen to the metabolic pool. The albumins are apparently more labile than certain globulins, and according to Allison different amino acid patterns favour the filling of one tissue compartment rather than another; one may be depleted while filling a second. Further, excess of one amino acid over requirements, e.g., me-

thionine, apparently reduces the retention of nitrogen. He reports that adding a large excess of methionine to casein in the diet will cause a loss of nitrogen from the skeletal tissues of the rat but will result in the building up of liver and kidney tissue. Feeding a protein source above an amount which produces miximum filling is obviously inefficient. It is perhaps a commonplace to state that all the constituents of the diet, including the minerals and water, play important roles in the maintenance, repair and growth of living tissues of which protein constitutes the bulk in all but the skeleton. When the caloric intake falls below 50 per cent of that which is adequate, the retention of nitrogen is markedly reduced.

In discussing the effects of the caloric level Allison refers to the work of Schwimmer et al.[21] who have apparently demonstrated in man that retention of nitrogen was obtained at an intake of only 900 calories if the nitrogen and fat contents were sufficiently high. Williams et al.[22] have reported that the retention of nitrogen in the rat was improved on a restricted diet if the fat content was high. These remarkable observations require confirmation and appear to run counter to earlier conceptions.

Allison also very rightly refers to the work of Benditt et al.[23] who found that the fabrication of a kg. of tissue in a growing rat and the reconstruction of a kg. of tissue in the adult protein-depleted rat demand the same quantities of structural material and similar constructing energies.

The contemporaneous changes in the serum proteins and lipids are also described by Peters. The early precipitate fall in albumin noted first by Cuthbertson and Tompsett[24] and confirmed by Peters[25] is coupled with a fall in lipid (Man et al.)[26] and obviously cannot be due to a general depletion of protein and lipid. Man has also shown that the serum amino acid nitrogen level also falls. These changes in albumin, lipid and amino acids happen only in patients who were previously in a healthy condition and are but further dislocations of the metabolic processes which Peters considers are characteristic of impairment of the synthesis of protein. If this is so, it is not plain why Peters contends that "in chronic debilitating conditions since the synthetic powers of the body appear to be intact, administration of generous quantities of protein with adequate calories should be a major therapeutic objective, and delay should not await the termination of the catabolic phases." It is not sufficient to know that "there is no evidence that the administration of large amounts of protein during the catabolic phase is injurious." Further account should be taken of the experience of Hirschfeld et al.[15] in burns when they found that the early administration of large amounts of protein to burned patients provoked nausea, vomiting, diarrhoea and other untoward symptoms. After the first few days their patients could tolerate larger intakes.

The pattern of events in protein depletion is not so clear cut as Allison outlines in his present contribution. For example, recent observations in Europe have shown that oedema may occur without a lowering of the plasma proteins much below the lower levels of what is regarded as normal. Allison points out that when an increase in α-globulin is found in the depleted animal this is due to a fall in the plasma volume rather than to an actual rise in α-globulin. A fall in plasma albumin and an increase in α-globulin appear to be associated with malnutrition, tuberculosis or cancer in man. When the α-globulin is reduced below normal in the protein-depleted dog, an increased susceptibility to infection results.

The cytoplasmic proteins of the liver are apparently the most rapidly mobilized of all proteins when animals are placed on a low nitrogen or protein-free diet. The production of haemoglobin, on the other hand, is sustained and when there is a real need for both haemoglobin and plasma protein, the protein flow in the animal depleted of blood and restricted in food protein favours haemoglobin formation.

THERAPEUTIC AND NUTRITIONAL ADVANTAGES OF PROTEIN HYDROLYSATES AND OTHER AMINO ACID MIXTURES

Turning from the physiology and pathology of protein metabolism to the subject under discussion, namely, the evaluation of protein hydrolysates and other amino acid mixtures, we must note that the evidence available does indicate that nitrogen equilibrium can be maintained and the protein requirements of normal animals, including man, can apparently be met by means of an intravenous infusion of properly prepared hydrolysates of efficient proteins. This has now been carried through for twenty-four days without mishap.[27] But there is no evidence that intravenous injection of such preparations is superior from a nutritive standpoint to the normal method of eating, and all evidence favours the normal route when that is available. Much poor physiology and wishful thinking have actuated some workers in this field, and the difficulty of administration of hydrolysates has been glossed over by many workers. If hydrolysates are not injected very slowly, they provoke nausea and vomiting. According to Madden et al.,[28] mixtures of pure amino acids might have advantages in that they can be injected more rapidly and in higher concentration without untoward reactions.

One of the great difficulties of the intravenous route is the large volumes of fluid that have to be injected over a long period of time. Peters points out that it is seldom possible to give as a hydrolysate more than the equivalent of 75 Gm. of protein and 300 to 400 Gm. of glucose, a total of 1,500 to 1,900 calories per day. These prolonged operations are distressing to the patient and thus adversely affect recovery. Peters states that even if hydrolysates are given slowly enough to avoid nausea, patients cannot be induced to eat while they are being injected. Meals generally must be relegated to the evening and therefore interfere with rest.

If the patient is able to ingest, digest and absorb sufficient food, there is no need to give some or all of it parenterally. When there is difficulty in ingestion, it may be necessary to provide highly nutritious fluid drinks, with skim milk as the main protein constituent. It has been recommended that when necessary advantage should be taken of the sense of thirst in order to secure adequate nutrition.

Peters finds no justification for the use of hydrolysates by mouth whether by ingestion or by tube, and he contests Co Tui's[29] contention that such preparations are more easily utilized than undigested proteins as being unsupported by physiologic evidence. With this the present writer is in entire agreement. The evidence of those who attempted to supply protein hydrolysates to gravely starved people in Holland and in Belsen Concentration Camp has shown that intact protein can be tolerated and utilized by these people. When intravenous therapy was necessary, plasma was the safest treatment.[42]

The observations of Riegel et al.[30] indicate that the excretion of faecal nitrogen is greater when hydrolysates are given than when whole proteins are given. Hydrolysates or amino acid mixtures fed intravenously cause an increased urinary excretion of amino acids and peptides, but usually this does not materially affect their nutritional value. On the whole, oral feeding of hydrolysates or amino acid mixtures is more efficient than intravenous feeding. The loss of amino acids and polypeptides through excretion in the urine is greater the higher the rate of infusion.

Peters draws attention to one useful application of intravenous hydrolysates, namely, when it is absolutely necessary to secure complete rest of the alimentary canal. In conditions such as acute mercury poisoning the evidence indicates that not even water should be taken by mouth. If complete rest can be achieved, this should end the characteristic vomiting and diarrhoea.

Homburger in his review very rightly stresses the difficulty in evaluating the nutritional status of a patient in respect to protein—one of the most complex of all

subjects. Some now consider that "the state of health" is a more embracing term, but the means of assessment are not thereby simplified. Homburger draws attention to the misleading interpretation which may arise from an assessment of protein depletion by analysis of the total plasma, albumin and globulin. As was pointed out earlier recent evidence has shown that protein depletion may exist without any marked depletion of these proteins.

It is pertinent to what has already been stated that Homburger in his review of the various types of hypoproteinemia gives little if any indication for the infusion or oral administration of protein hydrolysates. When protein has to be infused, it is recommended that plasma be given unless there is a complicating anaemia for which a blood transfusion would be the best line of treatment.

Allison points out that acid hydrolysis of protein destroys tryptophan and, to a much lesser extent, sometimes methionine and that there is also a destruction of certain essential polypeptides. Alkaline hydrolysis leads to marked racemization and cannot be recommended. The work of Chow, Allison and White[31] has shown that the utilization of casein by the dog and rat is not altered by enzymic hydrolysis, the hydrolysate having the same growth value in dogs and rats as the unhydrolyzed casein. A 60 per cent enzymic hydrolysis does not alter the streptogenin content which is essential for proper utilization.

One of the difficulties encountered by the reader of a series of seminars on a debatable topic dealing with treatment, such as the one under discussion, is to discern the wise procedure when experts differ. Young in his contribution to this symposium clearly indicates that the intravenous route should be chosen only when other methods of feeding are impossible. He adds that the best protein hydrolysates still do not permit convenient administration of the large amounts of nitrogen indicated in many postsurgical cases. Young then proceeds to comment on chemical considerations in the selection of protein hydrolysates.

The proteins which are mostly used for the production of hydrolysates are casein, lactalbumin, muscle, blood, liver and yeast protein but sometimes a mixture is used. The resulting product must of course be non-antigenic and have a low concentration of dicarboxylic amino acids as these are held to be nausea-provoking. Stability in solution and availability for infusion at a rapid rate are also necessary attributes. Furthermore, there must be an adequate energy intake to permit optimal use being made of the hydrolysate. In the writer's view it is doubtful if much attention need be paid to the vitamin side if the emergency requiring this intravenous feeding only lasts a few days.

This writer does not agree with Young's summary of the advantages to be gained by hydrolyzing proteins for oral use for so far no real evidence has been adduced that the hydrolysates by mouth are to be preferred to intact protein in cases of impaired digestion. As has been discussed earlier some doubt exists as to the real basis of the enthusiastic reports of Co Tui on the use of oral hydrolysates. Although they are as a rule completely soluble, the unpleasant taste or nausea-provoking attributes of oral hydrolysates are such as to undo the possible benefits to be derived from their complete solubility. Young later stresses the disadvantages of hydrolysates but it would have been better had he weighed these against the possible advantages and given a considered judgment. There is no doubt but that all protein hydrolysates marketed should have the information which Young advises clearly marked on their labels.

Werner in his seminar dealing with the problems of parenteral nutrition wisely points out that it is still debatable whether the results of routine parenteral feeding warrant the risks and discomfort to the patient as well as the expense. Werner's own work has shown that protein hydrolysates given in the postoperative period to patients undergoing subtotal gastrectomy for peptic

ulcer provide no definite evidence of a gain over a control series of patients treated exactly the same way but without the parenteral nitrogen. Werner draws attention to the effect on nitrogen balance of accidental or unavoidable interruption of parenteral feeding and points out that the extent of the caloric intake which must be provided with protein has not been entirely settled.

After prolonged periods of undernutrition the existing depletion of nitrogen stores may lead to hypoproteinaemia due to inability to meet the increased demands for nitrogen associated with operation. All the indications are that repletion is more readily accomplished before operation, that is, before the postoperative catabolic period ensues. The indications for parenteral feeding are inability to ingest, digest or absorb adequate quantities of food over a period of time which jeopardizes the chance of an uneventful convalescence or may even prejudice survival.

Werner considers that the rationale for employing the parenteral route before operation when oral or tubal feeding of intact protein is not available rests more on the necessity to restore liver function and to facilitate adaptation to a more vigorous nitrogen turnover than on the need for building up a store of nitrogen. It is admitted that the amounts of nitrogen retained during such treatment are quite limited due to the inadequate provision of calories. But this type of therapy is probably justified, especially in conjunction with plasma or whole blood.

In his discussion of proteins available for infusion Werner points out that when human plasma, whole blood or serum albumin are given intravenously to restore the blood volume and osmotic relationships they are also available for nutrition. If it is hard or impossible to sustain an adequate energy intake, the attempt to restore the circulating proteins and tissue proteins should be made as short as possible, otherwise, the patient's condition may deteriorate still further.

The present writer is not at all certain of the soundness of Werner's argument when he advises that once the parenteral administration of high nitrogen levels has begun, either before or just after operation, they should be continued for the first few days after the operation or otherwise the sudden discontinuance or reduction of the nitrogen intake for one or two days will result in sharp losses due to the fact that the nitrogen excretion continues at the same level as if the high intake had continued. While that may be so, the evidence indicates that the organism is geared in a catabolic or anti-anabolic phase immediately following injury. Further, the evidence does not fit Werner's statement that reduction in calory and protein intake after injury, plus the added demands of both during the febrile period, probably explains in large part the protein catabolic period. I would agree with Werner in his view that the use of hydrolysate and amino acids by vein should at first be limited to those postoperative patients in whom previous protein depletion has occurred and cannot otherwise be replenished preoperatively, and secondly to those in whom evidence of a postoperative complication has already appeared.

The rate of disappearance of plasma proteins from the blood stream to the tissues diminishes as the tissue stores are replenished. Werner finds that nitrogen balance studies reveal a great difference in the ease with which nitrogen given as preformed plasma or as red cell protein provides a positive balance as compared with nitrogen given as split protein in the form of hydrolysate or amino acids,[32] the difference being due to the increased excretion of nitrogen with the latter. This difference is apparently comparable to that seen when serum protein or whole blood is given by mouth.

While the lag in excretion of intact protein by vein results in greater efficiency of utilization than can be obtained by amino acid mixtures, Werner considers that there is evidence that the provision of a flow of amino acids to the liver is essential for

the maintenance of normal liver function. The lipotropic action of these substances, especially methionine, is apparently not obtained when preformed serum protein is injected.[34] The fatty liver of starvation is prevented or alleviated by food protein by mouth or by parenteral hydrolysates but not by intravenous blood or plasma and, according to Varco,[35] blood or plasma by vein fail to prevent death of semistarved patients following extensive and prolonged surgical operation. Nevertheless Varco has presented evidence in support of his view that the ingestion of protein as a preoperative preparation is as effective as, or more effective than, corresponding increments made available to the patient in the posttraumatic interval. The writer believes that there is some merit in Kremen's[32] suggestion that a mixture of plasma and hydrolysate or amino acids might be useful.

It should be noted that cardiac or renal dysfunction or both together may prevent toleration of intravenous feeding. Reactions to parenteral hydrolysates are few if pyrogens are removed, and the infusion tubing is renewed or treated with sodium hydroxide. As already mentioned nausea and vomiting may result from too rapid an infusion rate and Werner advises rest periods after infusion and the introduction of not more than 50 Gm. amino acid mixture at any one time.

Elman prefaces his article, the final one of the series, with a plea for clarity and uniformity in nomenclature when describing preparations for clinical use. He prefers that the term 'amino acid mixture' be used to include both the pure crystalline material on the one hand as well as protein hydrolysates (or digests) on the other. This term would thus also include mixtures of amino acids and peptides. One reason for using the term amino acid mixture in place of protein hydrolysate is that it would exclude gelatin which is not really a hydrolysate but is slightly hydrolyzed owing to the method of its extraction. Elman would retain the term hydrolysate to preparations in which the digestion has been carried out for purposes other than the production of amino acids or small peptides for nitrogenous nourishment. It is doubtful if Elman's suggestion will bear much fruit.

Elman provides an excellent historical summary of the development of these various amino acid mixtures produced by compounding mixtures of amino acids in both the natural and racemic forms and of enzymic and acid digests. In some preparations larger fragments have been removed and in one, aspartic and glutamic acids are removed and the product lyophilized. It is pointed out that as these amino acid mixtures act as a buffer, the pH of the mixture should be adjusted so as to have no really significant action on the acid-base balance.

That nausea and vomiting may also be caused by unnatural amino acids has been shown by Howe et al.[36] in dogs; particularly was this the case with *d,l*-methionine. Glycine improved the tolerance. It appears that mixtures of the essential amino acids and glycine can be tolerated at faster rates of infusion than with actual hydrolysates. But certain peptides or larger fragments may be necessary or beneficial to man in the long run. Elman points out that the evidence indicates no difference in nitrogen balance between a partial protein hydrolysate containing 75 to 83 per cent of its nitrogen still as peptides when injected and a complete hydrolysate injected at the same minimal level, and this even in spite of the large excretion of peptides and amino acids with the partial hydrolysate. Elman considers that this indicates that something was present in the retained part of the partial hydrolysate which improved nitrogen balance. The work of Christensen et al.[37] suggests that the peptides of a casein hydrolysate (amigen) appear to be less readily utilized by the tissues and more poorly retained by the kidneys than pure amino acids. Both sets of observations require confirmation. There is some unconfirmed evidence that the peptides from a partial acid hydrolysate are more efficiently utilized than those from an enzymic hydrolysate.

Elman rightly points out that since all the amino acids that go to form body proteins are essential to the body it is preferable for an amino acid mixture (or digest) to have both dietary essential and unessential amino acids present for maximum efficiency.

According to the work of Kade et al.[38] and Silber et al.,[39] the intravenous route in the dog is as satisfactory as the oral route as far as nitrogen balance is concerned, whether the test is with crystalline amino acids or with a hydrolysate. But in man it has been found that a lyophilized acid hydrolysate of casein gave better nitrogen balance when given by mouth than when injected. This is what one would expect from animal experimentation. It would appear wise when dealing with acid hydrolysates to fit the hydrolytic method to the protein concerned. According to Kozoll and Mok,[40] a 1,000 calory intake was optimal for nitrogen balance, and intravenous feeding beyond this did not improve utilization.

Casein hydrolysates are sometimes used at 5 to 10 per cent concentration and mixtures of pure amino acids at 8 per cent. In ten healthy males Werner was able to substitute 60 of the 90 Gm. of protein in the diet with an intravenous amino acid mixture with no change in the nitrogen balance. The subcutaneous route seems to be feasible for both pure amino acid mixtures and hydrolyzed protein. Indeed Madden et al.[41] thought that this route in the dog was better than the intravenous route. The intraperitoneal route is definitely unsatisfactory.

Elman routinely uses 100 Gm. each of amino acid mixture and 100 Gm. glucose in 2,000 cc. solution containing about 5 Gm. sodium chloride. This he gives in two 1 L. injections as 5 per cent hydrolysate and 5 per cent glucose, one in the morning and one in the afternoon or evening. Each injection usually takes two hours. This seems a reasonably safe procedure. Parenteral vitamins are injected as required. Attention is drawn to the tendency toward venous thrombosis and glycosuria which may result if 10 per cent glucose is used for infusion. Glucose, 5 per cent, in normal saline is well tolerated, however, but this means that considerable volumes are required to make up the energy intake required in the twenty-four hours. Use of fat emulsions for intravenous work is still in the trial stage and there are grave difficulties and dangers.

Werner and Elman both draw attention to the necessity of taking account of the electrolyte content and its relationship to the source of the protein hydrolyzed. Thus, hydrolysates from animal cells contain much potassium and magnesium; fibrin and casein hydrolysates contain relatively little salt and that mainly sodium.

When the use of hydrolysates is indicated, it is necessary to ensure that the protein used is a complete source of all the essential amino acids. The presence of polypeptides tends to limit the tolerance and speed of administration. It is not quite certain how necessary these larger fragments are to man as most experiments with pure amino acids have been of relatively short duration. When hydrolysis is practically complete and any deficiencies have been made good, it is apparently possible to infuse at a rate comparable to that at which glucose itself can be given. If only the laevorotatory forms are given, economy in material is considerable as the unnatural forms are usually inactive physiologically unless they are converted into the natural isomerides.

Elman agrees that the calory requirements are but inadequately met by such a parenteral diet. But is it wise to leave the rest of the energy needs to be met by adipose tissue? Elman considers that further evidence has confirmed that this is safe and he advises that for short periods of time at least the glucose intake can be safely limited to 100 Gm. Ketosis does not arise. Such a low calory intake obviously will not lead to the deposition of much tissue protein, but it will minimize the metabolic loss of protein. Elman freely admits that full tissue repletion can probably be achieved only through normal oral feeding. The need for parenteral amino acid mixtures is

frequently coupled with a need for blood or plasma.

There does not appear to be any real evidence that hepatic disease is a contraindication to the injection of amino acids. Elman would extend the use of amino acid mixtures, including hydrolysates, but the present author does not concur in this unless other means of nutrition are denied the patient.

Elman concludes by pointing out that protein hydrolysates and pure amino acid mixtures are utilized by the body and can be given safely by vein in all conditions in which one would in the past have had to inject glucose as a necessary source of nourishment. Suitable patients include those who are unable to ingest, digest or absorb sufficient food over a period of time or who must secure complete gastrointestinal rest. It is stressed that there must be clear proof that such rest is absolutely necessary.

SUMMARY

Available evidence indicates that nitrogen equilibrium can be maintained and the protein requirements of normal animals, including man, apparently met by intravenous infusion of properly prepared hydrolysates of biologically efficient proteins. But there is no evidence that the intravenous route is superior from the nutritive standpoint to the normal method of feeding. Indeed, if hydrolysates are injected too quickly, nausea and perhaps vomiting may lead to less efficient use of the amino acids and peptides. It is seldom possible to give routinely more than the equivalent of 75 Gm. protein and 300 to 400 Gm. glucose by the intravenous route. There does not appear to be any solid evidence for the use of hydrolysates orally or by tube into the alimentary canal.

While there is abundant evidence of the life-saving benefits which immediately accrue from the use of whole blood or plasma, these proteins also serve as a source of nutrition. There is some doubt whether the intravenous use of intact proteins will permit certain effects which are bound up with intermediary metabolic changes which follow the ingestion of protein in the food or the infusion of amino acid mixtures by vein. Mixtures of pure amino acids lack certain peptide fragments which may be necessary for growth and the full maintenance of nutrition. To save body protein it may be wise to include all the amino acids rather than to rely on the essential amino acids plus glycine.

The rationale for employing amino acid mixtures parenterally in place of, or along with, intact blood proteins rests more on the necessity to sustain liver function and to maintain a more vigorous nitrogen turnover than to the need for building up a store of nitrogen. This line of treatment may be worthy of further exploration.

Because of the difficulty of infusing sufficient protein and energy in the infusion fluid, it is generally agreed that it is not possible to make good the requirements of the protein-depleted organism entirely by intravenous injection. It is not wise to give fluid containing more than 5 per cent hydrolysate and 5 per cent glucose. Mixtures of pure amino acids may be given at 8 per cent strength. Even these levels necessitate some four hours to provide 2,000 ml. The whole procedure causes discomfort if not actually distress to the patient and also prevents rest. The calory requirements are but inadequately met by these procedures although it is held that for short periods of time the glucose intake can be safely limited to 100 Gm., the rest of the energy needs being met from the adipose tissue and the 100 Gm. of hydrolysate preventing further protein loss. More corroborative evidence is required on this fundamental issue.

It may be wise to restrict the use of intravenous hydrolysates and mixtures of pure amino acids to postoperative patients with previous protein depletion which has to be corrected preoperatively and sustained postoperatively, and secondly to those in whom evidence of a postoperative complication has already appeared.

Amino acid mixtures including hydrolysates are of value in treating conditions in which it is absolutely necessary to have complete rest of the alimentary canal, for example, in acute mercury poisoning.

Indications for parenteral feeding are inability to ingest, digest or absorb adequate quantities of food over such a period of time as to jeopardize the chance of an uneventful convalescence and which may even prejudice the chance of survival.

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Clinic on Psychosomatic Problems

Feeblemindedness or Pseudoretardation?

THE clinics are designed to bring out psychosomatic relationships both in symptomatology of the patient and in the organization of the hospital. Reports are directed by Drs. Stanley Cobb and Allan M. Butler and are edited by Dr. Henry H. W. Miles. This is a report of a staff meeting of the Pediatric-Psychiatric unit of the Massachusetts General Hospital. The preparation of these psychosomatic case histories receives support from the Josiah Macy, Jr. Foundation.

DR. SAMUEL KAPLAN: David J. (Unit No. 593549), a seven and one-half year old boy, was referred to the Pediatric-Psychiatric Service by a psychologist who had examined him and found evidence of mental retardation but was puzzled as to the cause of the intellectual deficit.

When the mother brought the patient to us, she asked primarily for advice on how to manage him and for an evaluation of his smallness of size. She described him as a very small, very "queer" boy who had developed slowly. She said that David always tried to compete with his bright twelve-year old brother and inevitably failed. He had been rather anxious during the previous summer which the mother attributed to his fears of failing in school. The mother also reported inconsistencies in his behavior. For example, he insisted upon having his parents dress him and at times feed him while in other ways he was precocious. He rowed a boat alone at five and helped to deliver newspapers at seven. At the time of referral David was attending a slow class in a public school where he was popular with his playmates.

Details of the family background were given by the mother, a thirty-eight year old professional woman, who was obviously tense and displayed a lack of appropriate emotion when discussing her husband's family and her son's difficulties. Her husband, she said, was a "tower of strength." He was a thirty-nine year old attorney who had never practiced law and who was employed as a sales manager. During the war years he had worked as a civilian employee of the Army and had been away from home for extended periods. The family had moved many times during those years.

There was a history of severe mental disturbances in the father's family. The father's mother, grandfather and two other relatives committed suicide and a younger brother became psychotic. In the mother's family a younger sister was said to have hysteria and the patient's maternal grandmother was described as a "cold" person. David's only sibling was the twelve year old brother who was apparently normal.

Past history revealed that the patient was born prematurely with a birth weight of less than 3 pounds. He had been in a precarious condition with cyanotic episodes and the mother was told that he probably would not live. At the age of three months he was again in a critical condition with bronchitis. After this he got along well and the motor aspects of his development seemed only slightly retarded. He sat alone, crawled at eight months and walked at eighteen months. However, he was markedly slow in his speech development and did not talk until he was four years of age.

The mother described the boy's background to our social worker and during this series of interviews a number of significant factors appeared. Although apparently anxious to help him, she nevertheless discussed him in a detached manner, referring to him as a "fascinating case study." The mother was superficially tolerant and affectionate and yet could not permit him to express any aggression. Her own hostility toward David was evident from various incidents which she discussed. As an example, she had once found it very difficult to tell him not to play

on a certain broken footbridge. She knew that if she had allowed it he would undoubtedly have been drowned.

The mother said her husband was overindulgent, overprotective and very affectionate toward David. However, he had been a shadowy figure during the first six years of David's life by reason of his long absences. The father currently was working until nine or ten every night and saw the boy only during week-ends. The mother had recognized David's concern over the absence of his father and reported that during the previous summer, when the family lived together as a unit for the first time, he had seemed puzzled as to the place of the father in a family.

The patient's brother was openly hostile and rejected him constantly. When David was three years old, the brother had been sick for almost a whole year and had required so much attention that David was more or less forgotten. There was a repetition of this sequence when David was five. The mother emphasized the marked jealousy that David expressed toward his brother. The past summer the mother had had to leave suddenly because of her father's illness and David had been "deserted" again.

Physical examination in the Children's Medical Clinic revealed nothing abnormal. The patient was small for his age but not unusually so and there was no evidence of any endocrine dysfunction. A neurologic consultant was unable to find any clinical signs of old brain injury. However, the electroencephalogram was definitely abnormal and Dr. Abbott will describe it for us.

Dr. John A. Abbott: This electroencephalogram is an abnormal record. It shows notably: (1) slow activity, diffuse, symmetrical and more marked posteriorly and (2) a paroxysmal breakdown in the first minute of overbreathing. In more detail, with normal breathing there is probably low voltage beta activity anteriorly; irregular and some regular at around 10 per second posteriorly; waves at about 2 per second and 100 microvolts posteriorly and other slow waves diffusely. With overbreathing there is breakdown in the first minute with bilaterally synchronous 3 per second paroxysmal activity to 125 microvolts anteriorly and ragged activity posteriorly.

Dr. Kaplan: The psychologic tests were very helpful and perhaps should be discussed at this point in the presentation.

Dr. Elizabeth M. Hincks: I first gave him a performance test, the Merrill-Palmer test. He had a mental age of five years three months and an I.Q. of 68. He showed up poorly in form and space relations. He seemed to enjoy the test and was cooperative. The next time I gave him a Stanford-Binet test. Then he had a mental age of five years nine months and an I.Q. of 75. He did not enjoy this test so much. At times when it seemed he did not know the answer, he talked in a silly fashion and almost "free-associated." When we got to the part about repeating numbers he said: "No more numbers" over and over. His language development was better than his ability in mechanical and spatial relations. He passed all verbal tests at five years, pictures at six years, sentence memory at seven years and similarities at age eight. He seems to have special defects for form and space, rather than memory and reasoning difficulty.

Dr. Samuel Waldfogel: The patient was given the Rorschach test and the following interpretation was made: Supporting the possibility of mental defect were the stereotypy, lack of any movement, apparent lack of shading and the appearance of several very poorly structured forms. However, in contradiction we found extremely rapid syntheses of the blot (usually the whole) several of which were quite adequate and the absence of oligophrenic details. It seemed quite possible that this boy's intellectual defect resulted primarily from an attentional deficiency. One might postulate that because of his extreme impulsivity he could make only brief and superficial contacts with his environment which on the one hand constantly attracted him and

on the other hand seemed to frighten him. Apparently he was neither able to control his own emotions nor make adequate relations to others. The complete loss of control on the polychromatic card indicated the extent to which affect was a disruptive influence in this boy and added evidence that his intellectual deficiency stemmed from his turbulent emotional life. The severity of this boy's personality problems, whether or not he was mentally retarded, could not be minimized and the possibility of some diffuse cerebral lesions had to be taken into account.

DR. KAPLAN: On the basis of the history of prematurity, neonatal cyanotic spells, slight retardation in the development of motor skills, marked retardation in acquisition of speech and the abnormal electroencephalogram, it was believed that the patient probably did sustain diffuse brain damage (either from hemorrhage or anoxia) at the time of birth. However, because of the obviously disturbing family relationships and the clues given by the psychologic tests we decided to study the psychogenic factors by means of weekly interviews in the Out-Patient Department.

At first David showed evidence of great tension. He was a small, wiry boy with a worried, old-looking face. He talked constantly and rapidly, running many words together, omitting syllables and using many infantile expressions. In contrast, however, he used many polysyllabic words quite correctly. Physically he was restless and overactive and the therapist sensed great anxiety in his speech and activity. During the early interviews David was much preoccupied with the subject of magic, emphasizing over and over his belief that one could accomplish things only by making use of magic. (His brother was an amateur magician and could make objects disappear.) He was very boastful, seeking praise constantly and at the same time being unable to tolerate the slightest criticism.

After about two months David's behavior changed. He became less active and there was slight improvement in his speech. It was then that he introduced two themes into the interviews. One of these, elaborated upon in great detail during subsequent visits, was his desire to eliminate his father from the home. The other was a wish to kill his mother, and this was dropped for a long time, only recently being expressed again.

The interviews very clearly illustrated David's wish to kill his father, his fear that the father would annihilate him in retaliation and his consequent overwhelming feeling of anxiety and insecurity. In one session David greeted the therapist by pointing a toy pistol at him and shouting: "Stick 'em up!" He "forced" the therapist at gun point into the office and then spent the next half hour "killing" him by a variety of means. His fertile imagination in this and other interviews was quite in contrast to the picture presented by a dull child. He pretended to throw the psychiatrist from a ship; he turned on a radiator saying that it was a jet of poison gas and devised other ways of punishing him. At the next interview he burst into the room shouting: "I'm the police. Who killed David's father? Did you? You did! I'm going to shoot you," and proceeded to do so. The therapist denied the accusation and reminded David that he himself had done so in play last week. This resulted in mounting anxiety and the opportunity was taken to explain that neither one had *really* killed David's father. The therapist went on to say that lots of little boys wished they could get rid of their fathers, and then they got terribly frightened because of their feeling that their father would punish them for this wish by killing them. David listened very attentively and then asked: "What would the father do? Would he kill the boy?" He was reassured that the father would understand and, since a wish is not a deed, the boy would not be punished at all. This sort of explanation was repeated several times and there was no more shouting and killing by David.

In subsequent interviews David again expressed ideas that his father might kill him and the only solution was to get rid of the father first. However, in his play he no longer acted out the killing himself, but

pretended to be the informer who called the police; he was then a gleeful onlooker as the police arrested and killed his father. More recently the object of his aggression has been the therapist rather than the father.

After about five months he returned to the theme hinted at in earlier sessions, namely, his wish to kill his mother and the fear that she would take revenge upon him. The latter element came out clearly during his play one day. He was acting out the rôle of the mother and went to the doll house and shot the baby doll with a toy cannon. (In previous sessions he had clearly identified himself with the baby doll and had given it the name of David.) In a subsequent interview the patient made the mother doll go up to the roof of the doll house to punish the baby for being there. He then "accidentally" pushed the mother off the roof and soon repeated the act. When the therapist remarked that the mother seemed to be falling, David picked up the doll again and said: "I'm going to throw her out of the window." He then repeated a former sequence: He cast the therapist in the rôle of David and he became the policeman who arrested David and executed him for killing the mother. Again he was reassured repeatedly that the mother was not really dead, that it was only his *wish* that she be killed, again emphasizing that the wish is not the equivalent of the act and is not punishable. He refused to accept this reassurance, and at the present time this problem is the central one in the therapy.

During the period of therapy (about six months) there have been definite changes in David. His speech has improved markedly and he has lost the air of tension and anxiety. He is more self-assertive and no longer needs help in dressing, eating, etc. He is doing well in school, is at the head of the slow class and is to be promoted. His attention span has improved to the point where he can now complete all of his school papers, something he could not do last term.

DISCUSSION

Dr. Nicholas D. Rizzo: His general behavior during the picture projection test was extremely impulsive. His associations were very hard to follow and at times his responses were not at all pertinent to the card shown. When we came to the picture of the male nude, he saw it through a window although there is no window in the picture. He spoke of many things but denied seeing the nude. When I showed the picture of the female nude, he almost snatched it from my hand. On the whole he dealt with the picture situation poorly and in the first part of the test he killed his mother in three of the pictures.

Dr. George Carter: In regard to the tests, does not his doing well verbally rule out mental retardation?

Dr. Hincks: I do not think we can call his mental age figure a flat fact at this time. When I saw him, without having heard all this, I thought there might be brain damage or something permanently wrong. This picture is not that of feeblemindedness. He seems retarded but not defective. His reasoning, vocabulary and memory are all very good. His rapidity of motion, the activity of his aggressive fantasies, the variety of things he thinks to do are all not in accordance with feeblemindedness. I would not make a diagnosis of intellectual deficit yet.

Dr. Carter: Do mentally defective children have so much anxiety?

Dr. Hincks: The borderline patients who have to compete with children of higher I.Q.'s get hysterical blindness sometimes. They get anxiety because they have to compete.

Dr. Allan M. Butler: They get hysterical temper tantrums when frustrated by their own incompetence.

Dr. Gertrud Reyersbach: Some appear to be retarded when they are slow in speech development but you cannot call them defective. Later they are able to talk very well.

Dr. Hincks: This boy felt rejected. He might not have had any incentive to talk before.

Dr. Butler: This is a fundamental problem in the value of the I.Q. If a boy has an I.Q. of 70 and yet you see the boy is not retarded but is emotionally blocked,

it limits the value of the I.Q. as a diagnostic factor. Certainly the psychologists ought to be refining the tests to make this important distinction.

DR. HINCKS: It is not the tests that need refining. You need an examiner and interpreter of the tests who has a great deal of experience and knowledge of these different types of children. An I.Q. may be an incorrect index of the mental capacity of the child.

DR. CARTER: Do you think a test invalid when you find scatter?

DR. HINCKS: Scatter might indicate brain damage, too. You have to take all the variables into consideration.

DR. STANLEY COBB: This is a very important case because it brings up the diagnostic differentiation: *amentia vs. dementia.* If the former, it is "lack of mind," a permanent and hopeless defect. If "dementia," it is more or less loss of a mind once present and the prognosis can be good. The tests for I.Q. given by Dr. Hincks showed a low score but were not typical of mental defect (amentia). Dr. Waldfogel's Rorschach test and Dr. Rizzo's picture test gave evidence that the child was emotionally disturbed and not "mentally defective" in the primary and hopeless sense in which that term is usually used. The history as learned by psychiatrist and social worker gives plenty of evidence that the boy was in a family situation which caused him to feel deeply rejected. Dr. Kaplan's patient therapy over six months not only improved the boy's emotional reactions and intellectual ability but also brought out more evidence that he felt rejected and was full of anxiety, fear, hate and guilt. In other words, his emotions were blocking his use of his perfectly serviceable mind. Thus we have a right to say that he has no "amentia" but a beginning and not too serious loss of ability to use his mind (dementia). There is no neurologic evidence that his brain is injured, but we cannot pass over the history of premature birth and cyanotic spells and the abnormality of the electroencephalogram without admitting that there may have been cerebral damage. Nevertheless, damage to the brain does not always, nor even often, cause intellectual defect. The brain has a great reserve and a brain injured in childhood may remain a perfectly serviceable organ for intellectual development. The child may not go as far as he might have with a perfectly normal brain; he may be more unstable; he may even become epileptic later. But the functional capacity of the brain remains within what we call normal limits, arbitrarily scored as I.Q. between 90 and 130.

That is what I think about this boy. He has a good enough brain to get along in the world if we only can relieve him of his emotional stress which is now blocking progress. Dr. Kaplan is making good progress.

The prognosis depends upon therapy. If our good team-work of psychiatrist, social worker and psychologist with patient and mother continues, I feel hopeful of a good result. If the treatment of child and mother is interrupted, the outcome may be disastrous. Children with as great a load of rejection and fear as this boy has may go into a regressive type of behavior that is said to become permanent. At least many sufferers from it seem to have become set in their ways and spent their lives in institutions for the mentally ill or defective. Heller* described extreme cases of this sort in 1908 under the name of *Dementia infantilis.* He speculated as to the various possible causes, but did not express his own opinion as to whether such cases were due to emotional stress, cerebral lesion or hereditary schizophrenia. Not much progress was made in the next thirty-five years, but recently Bender in New York, Putnam and Rank in Boston and Yakovlev in Connecticut have discussed these cases. It is obvious that somewhat similar clinical pictures can occur from each of the three causes mentioned. The present need is for better diagnostic methods and more clinical acumen. Then the patients with good prognosis can be

* HELLER, T. Über Dementia infantilis (Verblödungsprogress im Kindesalter). *Ztschr. f. d. Erforsch. u. Behandl. d. jugendl. Schwachsinns,* 2: 17, 1908.

chosen for therapy and those who are hopeless patients sent to custodial institutions.

DR. LUCIE JESSNER: Observation and treatment of this boy, who has a family background of serious mental disturbance and signs of brain damage shows the interrelation of various factors producing a psychiatric disturbance. Fifty years ago one would have probably made a diagnosis of retardation on the basis of brain damage and would have considered psychotherapy futile. Psychologic tests showed good reasoning powers in spite of disturbances in special fields and revealed the strong factor of anxiety in his performance. Psychiatric study showed the influence his life experience had in creating uncertainty and confusion—a child rejected by his mother who consciously wished to kill him and lacking the presence of his father in most of his earlier years. In psychiatric interviews his fear of being killed and robbed of his penis are expressed. It is not surprising that in this atmosphere of hostility he is unable to restrain his own aggression. Being aware of his own dangerous impulses, his anxiety increases because he expects punishment for his intentions. In psychotherapy he was allowed to express his feelings in words and in play and was informed and reassured about the difference between doing something "bad" in fantasy and the actual carrying out of such a threat. He has shown a remarkable improvement in his speech and I believe that this is due to the fact that he learned with Dr. Kaplan that he can tell in clear words what he thinks without being punished for it. His behavior on the whole seems less fearful and erratic. It seems most desirable to continue treatment, as this boy in spite of his central nervous system disturbance is capable of developing. It also seems important to continue working with the mother toward the goal of accepting this child.

SUMMARY

This case was presented to illustrate a not uncommon problem in the field of child psychiatry. A boy who is a "retarded" child was referred for evaluation of his apparent intellectual deficit. The history and the abnormal electroencephalogram furnished some evidence that he had suffered neonatal brain damage. This in itself could account for the clinical picture but on more careful scrutiny of the family relationship, certain factors were noted: the patient's rejection by his mother, the years of early life when his father was literally a missing figure in the family, and the long periods of neglect due to the brother's sickness.

The Rorschach test was of help in clarifying the problem as it indicated much anxiety and a severe personality problem in addition to the possibility of diffuse brain damage. It was brought out in the discussion and is worth re-emphasizing that the I.Q. is not always a correct index of the mental capacity of a child. The retardation may be due to severe emotional disturbances rather than feeblemindedness.

Psychiatric interviews confirmed the suspicion that the patient was a very insecure, anxious and emotionally disturbed child. During six months of therapy he showed a capacity for change and development. It was therefore believed that the mental retardation was not due primarily to innate lack of capacity but was largely a "pseudo-retardation" caused by an emotional disorder. Two conditions apparently existed: (1) cerebral damage dating back to birth and (2) superimposed neurotic disturbance. One might regard the brain damage as one of life's handicaps with which the patient must contend. His progress in psychotherapy has been encouraging thus far and further improvement is anticipated.

The technics used in psychotherapy with children will not be described here as good discussions are available.* The interview material, however, was cited in some detail to bring out certain points. Once a good relationship has been established with the child, one can learn a great deal from observing his play. The "acting-out" of

* WITMER, H. L. Psychiatric Interviews with Children. New York, 1946. The Commonwealth Fund.

fantasies by means of dolls or by assigning roles to patient and therapist is extremely helpful. This boy expressed very clearly the common childhood belief in magic and in the "omnipotence of the wish." One can thus understand the tremendous anxiety with which he was burdened. It is important to note that reassurance is not given indiscriminately, but is given along with an explanation that the child's specific fears are not really true. In this case, the wishes that the parents should die were acted out very clearly and thus explanation and reassurance could be given with confidence.

Clinico-pathologic Conference

Diabetes, Fever of Unknown Origin and Coma*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, C. S., (B. H. No. 143684), was a fifty-six year old, white married housewife who entered the Barnes Hospital on February 4, 1947, complaining of chills and fever. The family history was irrelevant but the past history was of interest in that the patient had been known to have diabetes for eight to ten years; for some of this period she had apparently followed a diabetic diet but had never taken insulin. Her general health had evidently been good until three years before admission when she had a febrile illness characterized by a temperature ranging from 101 to 104°F., associated with chills. The episode lasted approximately six weeks but no diagnosis was established. The patient resided in a small town in Illinois and frequently visited relatives in the nearby countryside where she drank well water and milk which was probably unpasteurized. During the winter prior to her admission to this hospital she had cleaned pheasants upon several occasions, the last time two weeks before entry.

Ten days prior to admission the patient developed malaise and her temperature was found to be 101°F. On the following day she developed pain in the flank which persisted. Her temperature elevation likewise continued at approximately 101°F. She refused medical attention for three days but then consented to enter the local hospital. During her hospitalization there she was given 40,000 units of penicillin every four hours but despite this therapy her temperature ranged between 101 and 103°F., and she had one or more chills daily. Three days before entry the patient became comatose, presumably because of the onset of diabetic acidosis. Information regarding laboratory studies at the outside hospital were as follows: On admission the urine sugar was said to have been 3+ but no acetone was present. The blood sugar was 250 mg. per cent. On the third hospital day the urine sugar was 4+ and the urine was positive for acetone. On the same day the white count was 7,800 but it subsequently fell to 3,600. Smears for malarial parasites were negative. The patient was given insulin therapy and glycosuria and acetonuria were said to have been controlled. Because her temperature continued to spike, she was seen by a consultant who advised immediate transfer of the patient to the Barnes Hospital.

At the time of entry the patient's temperature was 40.3°C., pulse 100, respirations 26 and blood pressure 164/80. The patient was stuporous and appeared acutely ill. Her face was flushed and the skin was generally hot and dry. Respirations were not labored but the patient groaned with each expiration. There were numerous ecchymoses, presumably the sites where insulin was injected. Although one or two suggestive petechial spots were noted, no generalized eruption was present. The pupils were small but reacted normally to

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light and accommodation. The eyegrounds were not remarkable. The nasal mucosa was slightly reddened and there was a small amount of bloody crusting in the left nostril. Examination of the mouth revealed the tongue to be quite dry. The throat appeared normal. The neck was not stiff. Examination of the lungs revealed them to be clear to percussion and auscultation. The left border dullness of the heart was percussed 9 cm. from the mid-sternal line in the fifth interspace. The apical impulse was prominent. The rhythm was regular and no murmurs were heard. On examination of the abdomen, although no organs or masses were felt, the patient's response to palpation of the left upper quadrant and left costovertebral angle indicated tenderness in those areas. Pelvic and rectal examination were negative. There was no lymphadenopathy or edema. The neurologic examination, aside from the stupor, was not remarkable.

Laboratory findings were as follows: Blood count: red cells, 3,470,000; hemoglobin, 9.7 Gm.; white cells, 5,750; differential count: stab forms, 12 per cent; segmented forms, 65 per cent; lymphocytes, 22 per cent; monocytes, 1 per cent. Urinalysis: specific gravity, 1.010; albumin, trace; sugar, negative; sediment, many white blood cells, a few in clumps, occasional red blood cell. Blood Kahn test: negative. Blood sugar: 127 mg. per cent; carbon dioxide combining power, 58.7 vol. per cent. Total protein: 5.6 Gm. per cent; albumin, 3.2 Gm. per cent; globulin, 2.4 Gm. per cent.

On admission to the hospital the patient was given 1,000 cc. of 5 per cent glucose in normal saline intravenously, and several hours later 1,000 cc. of ⅙ molar sodium lactate containing 5 Gm. of sodium sulfadiazine were given intravenously. Penicillin, in a dosage of 40,000 units every three hours, was begun. On the morning following admission the patient was still obtunded; she was restless and groaned frequently. Her temperature was 40°C. She was given insulin, glucose in saline and sulfadiazine parenterally. A blood culture which had been obtained on admission was reported to show a moderate growth of coliform organisms; the same organisms were also isolated from the urine culture. When the non-protein nitrogen was reported as 77 mg. per cent, sulfonamide therapy was discontinued and streptomycin therapy instituted. During the course of the day the patient continued to be stuporous and hyperpyrexic. A lumbar puncture was performed and the initial pressure was found to be 116 mm. of water. The fluid was clear and contained only 8 cells; the protein was 20 mg. per cent, the colloidal gold curve normal and the Wassermann negative. Further blood studies revealed the red count to be 3,640,000 with 8.7 Gm. of hemoglobin. The white cell count was 8,050, the differential showing 25 per cent stab forms, 65 per cent segmented forms, 7 per cent lymphocytes and 3 per cent monocytes. The polymorphonuclear leukocytes showed marked toxic granulation. A second blood culture obtained at this time was likewise positive for coliform bacilli. During the afternoon of the second hospital day the patient's pulse became rapid and thready. She was placed in an oxygen tent and given a whole blood transfusion. Although she continued to be stuporous, she did respond to painful stimuli. Her temperature remained at 40°C. By 5 P.M., despite administration of insulin, the blood sugar, which in the morning had been 382 mg. per cent, had risen to 443 mg. per cent. The urine sugar was 4+ and the urine was positive for acetone. The sediment showed only an occasional white cell and 3 to 5 red cells per high power field, and 1,000 cc. of ⅙ molar sodium lactate was administered intravenously; 20 units of insulin was given every two hours—the urine sugar was carefully followed at frequent intervals. By 7 P.M. the blood sugar had fallen to 337 mg. per cent. By the early morning hours of the third day the urine was sugar-free.

On examination the morning of the third day the patient was still stuporous. Her

blood sugar, drawn at 8 A.M., was 211 mg. per cent. The non-protein nitrogen had risen to 80 mg. per cent. Another blood culture was drawn and subsequently was reported positive for coliform organisms Examination of the urine at noon showed 4+ sugar, no acetone and the centrifuged sediment showed only a few white cells. Agglutination tests for typhoid were negative. During the course of the afternoon the patient's respiratory rate increased and her respirations became more shallow. Examination of the lungs was essentially negative. Re-examination of the heart revealed a grade II apical systolic murmur and an occasional ventricular premature contraction. The patient was not cyanotic but slight edema of the hands had appeared; likewise, minimal pitting over the sacrum was noted. The abdomen was moderately distended but soft. The liver did not appear to be enlarged. Tenderness in both flanks persisted; it was much more marked on the left where there was definite resistance to palpation. The kidneys could not be felt. During the course of the day constant attention was paid to the patient's diabetes which was kept under control. In addition to insulin she received a second blood transfusion and 1,000 cc. of 5 per cent glucose in water. Despite all supportive measures, however, she failed to regain consciousness and she expired at approximately 10 P.M. on February 6, 1947, the third hospital day. Her temperature had remained at approximately 40°C. throughout the last day of life.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Upon admission to the Barnes Hospital, this patient was indeed profoundly ill. She was admitted in a stuporous state and never fully regained consciousness; her condition was complicated by the presence of colon bacillus bacteremia. Dr. Schroeder, in view of the apparent localization of tenderness to the left flank and the fact that colon bacilli were recovered from both the blood and the urine, would you not agree that the patient probably had infection of the left kidney or of the area about the left kidney?

DR. HENRY A. SCHROEDER: Yes, I should certainly think so.

DR. ALEXANDER: Do you not think it possible that the illness which occurred three years prior to admission, which was characterized by chills and fever of six weeks' duration, may have represented renal infection?

DR. SCHROEDER: That suggestion seems to me to be a good one although we have insufficient information about the episode to be certain.

DR. ALEXANDER: Would you care to suggest the lesion in the kidney? Do you believe that there was a severe enough infection to lead to renal insufficiency? As you recall the patient's non-protein nitrogen was significantly elevated.

DR. SCHROEDER: I am not sure that I can identify the pathologic lesion. The patient's blood pressure when she came to the hospital was only slightly elevated and she apparently was excreting urine satisfactorily. I believe that to explain azotemia one would have to assume that there was either previous renal damage or else the acute renal infection was bilateral and quite severe.

DR. ALEXANDER: It would seem likely to me that if elevation of the non-protein nitrogen were due to renal disease then both kidneys would have had to be involved. Dr. Futcher, do you think that the azotemia could possibly have been prerenal in origin or would you rather ascribe it to definite renal insufficiency *per se?*

DR. PALMER H. FUTCHER: I believe that there was almost certainly primary renal insufficiency, but there may have been contributing prerenal factors. The patient's diabetes apparently had not been fully controlled and she was probably dehydrated. Furthermore, in a poorly controlled diabetic there is probably increased breakdown of protein and therefore an additional amount of nitrogen to be excreted; if renal function was already impaired, this incre-

ment might assume significant proportions. Finally, on the basis of long-standing diabetes the patient may well have had intercapillary glomerulosclerosis.

DR. ALEXANDER: In other words, you believe that the patient may not have had acute infection of the kidneys alone, for example, abscesses or pyelonephritis, but that possibly she had vascular disease as well.

DR. FUTCHER: I would be inclined to think that most of the nitrogen retention resulted from the acute infection, but I believe that intercapillary glomerulosclerosis and/or pyelonephritis were probably present and of significance. Of course, there are other possible renal lesions associated with diabetes, and particularly we should mention necrotizing renal papillitis which has been described in diabetics. It occurs in association with acute pyelonephritis and is characterized by necrosis of the renal papilli. As far as I know the syndrome almost invariably leads to a fatal outcome.

DR. ALEXANDER: That is a very good suggestion. Certainly we can say that this patient's kidneys may well have been markedly involved by one of the acute disease processes mentioned. This patient, as we have noted, had bacteremia due to one of the coliform bacilli; she received large amounts of penicillin, sulfonamides and streptomycin, all apparently to no avail. Which of these agents, Dr. Harford, would you consider most effective in treating overwhelming colon bacillus infection?

DR. CARL G. HARFORD: Streptomycin would be the drug of choice in this situation. It is of interest to point out that the organism which was recovered from this patient's blood was studied and found to be sensitive to 5 micrograms of streptomycin per cc. but not to 4.

DR. ALEXANDER: You have been quoted on occasions as stating that sulfadiazine is an effective drug for the treatment of colon bacillus infection of the urinary tract. Would you comment on this point?

DR. HARFORD: There are certainly exceptions, but in many cases sulfadiazine in adequate dosage controls such infections quite well.

DR. ALEXANDER: This patient, Dr. Wood, had had a high, unexplained fever when she first entered the hospital in her home town. Although no diagnosis was established, she was given penicillin for several days without response. At present the custom of giving chemotherapeutic agents in the presence of fever, even though a diagnosis is not established, is rather widespread. Would you comment on this practice?

DR. W. BARRY WOOD, JR.: That such a procedure may be very dangerous is illustrated by this case. It would seem to me that the physician's first responsibility is to attempt to determine the cause of the fever and to do so he should utilize all the diagnostic aids at his command. Whether one can justifiably call fever "unexplained" depends upon the effort that has been made to reach a diagnosis. In this particular case it seems in retrospect that the diagnosis of urinary tract infection might have been made more promptly and the organism isolated. Had that been done when the patient first presented herself to the outside hospital, she could have received more definitive treatment and might have made a more favorable response. We should make every effort to reach a specific diagnosis in cases of undetermined origin rather than depend upon the "shot gun" use of chemotherapeutic agents.

DR. ALEXANDER: I think your point is very well taken, but we have all seen patients whose condition was critical at the time of entry and since the results of many diagnostic procedures may not be known for several days do you think that penicillin, being the least dangerous drug, would be the agent of choice in such a situation?

DR. WOOD: I believe it is fair to say that penicillin has the widest range of application. It would probably be beneficial in more infections than would streptomycin and it is considerably more potent than the sulfonamides. Furthermore, as you have pointed out it is relatively non-toxic. How-

ever, if I were faced with the problem of treating a patient critically ill with signs of an infection in whom the specific diagnosis was unknown, I would give both penicillin and streptomycin. Had that been done promptly in the case under discussion the outcome might have been different.

DR. ALEXANDER: You would give penicillin and streptomycin but would not employ sulfonamides.

DR. WOOD: Yes. When I made the foregoing statement several days ago, Dr. Carl V. Moore correctly reminded me that there is at least one infection in which streptomycin and a sulfonamide are more effective than streptomycin and penicillin, namely, in acute brucellosis. Therefore, if one suspects undulant fever, one should probably use streptomycin and sulfadiazine; otherwise, I would tend to avoid the sulfonamides. We have discussed in these conferences during the past few years a number of fatal cases of sulfonamide intoxication.

DR. ALEXANDER: Would you comment on the use of penicillin by mouth? Is it effective by that route?

DR. WOOD: One has to give by mouth approximately five times the indicated parenteral dose to achieve the same results in terms of blood concentration. However, there are some patients who absorb penicillin poorly from the gastrointestinal tract and in such patients one often does not achieve an adequate blood level. Certainly when a patient is acutely ill, it seems much more advisable to give the drug by the parenteral route.

STUDENT: I should like to ask Dr. Wood if he thinks that sulfonamides are preferable to penicillin in the treatment of meningococcal meningitis.

DR. WOOD: Your question is a good one. I would agree that in meningococcal meningitis sulfonamide therapy is probably just as effective as penicillin; indeed, there are those who believe that it is even more effective because of its prompt diffusion into the cerebrospinal fluid. The diagnosis, however, of acute bacterial meningitis usually is not too difficult and rarely need be considered among the "fevers of unknown origin." On the other hand, chronic meningococcemia does constitute one of the causes of unexplained fever. In that instance I would prefer to use penicillin because in chronic meningococcemia the focus of infection is not in the subarachnoid space but rather at a site elsewhere in the body where penicillin should be effective.

DR. ALEXANDER: To return to this case I gather that this patient actually was in a coma or in a semicoma for almost ten days before entry to the Barnes Hospital.

DR. JOSEPH C. EDWARDS: That is correct. I was called to see this patient in consultation at the outside hospital. At that institution there were no facilities for doing blood cultures. Our advice was that she be brought immediately to the Barnes Hospital and she was transferred without further delay.

DR. ALEXANDER: When you first saw her, did you have the impression that she was in diabetic coma?

DR. EDWARDS: Yes. In view of her history diabetic coma was one of the first diagnoses I considered, but when she failed to respond to adequate control of acidosis I assumed that there was a complicating urinary tract infection. The urinary tract involvement was suggested not so much by the urinary findings which, when I first saw her were not too striking, but rather by the physical findings which included tenderness in the left costovertebral angle. The fact that she remained obtunded despite control of her diabetes led us to consider bacteremia seriously, and for that reason a blood culture was taken immediately upon admission to this hospital. Penicillin and sulfonamide therapy were given in an attempt to combat the suspected infection, and we awaited the results of the blood culture and other laboratory data before proceeding with further treatment.

DR. ALEXANDER: When the report of the positive blood culture was made, did you think that her obtundity was due to bacteremia?

DR. EDWARDS: Not entirely. We worried about central nervous system involvement and therefore performed a lumbar puncture which, as you already know, was negative.

DR. ALEXANDER: Does the finding of normal spinal fluid exclude the presence of a brain abscess?

DR. EDWARDS: No, not in the early stage of the illness.

DR. ALEXANDER: Dr. Schroeder, do you believe that the stupor was due to uremia?

DR. SCHROEDER: No, I do not think that the non-protein nitrogen was high enough to produce coma by itself. Rather I would think that there was an additional factor, probably the bacteremia.

DR. WOOD: When I saw the patient with Dr. Edwards after her arrival in this hospital, I believed that bacteremia in itself was sufficient to explain the stuporous state. Stupor or coma may result from severe bacteremia. In addition, in this patient there were also other factors such as the uncontrolled diabetes and the urinary tract infection itself.

DR. CARL V. MOORE: I would like to ask Dr. Harford whether a pulse of 100 with a temperature of 40°C. seems entirely compatible with any of the diagnoses suggested.

DR. HARFORD: One possible explanation for bradycardia may lie in the absorption of an endotoxin elaborated by the infecting organism, a situation possibly analogous to that in typhoid fever.

DR. WOOD: I think Dr. Harford's point is very well taken. The endotoxins of various gram-negative bacilli may certainly cause bradycardia. Colon bacillus bacteremia may similate typhoid fever; you will recall that this patient also exhibited leukopenia, common in typhoid. Bacteremia due to the Salmonella suipestifer, another gram-negative rod, may likewise produce a clinical picture indistinguishable from typhoid fever as was emphasized some years ago by Dr. A. M. Harvey in an excellent review of suipestifer infections.[1]

DR. FUTCHER: In regard to the comatose state I have seen one patient and heard of another who, in the course of treatment for diabetic acidosis, received unduly large doses of insulin and as a result developed hypoglycemia for a period of several hours. Subsequently, although the hypoglycemia was corrected, these patients failed to recover consciousness, developed hyperpyrexia and died. Is it possible that this patient's diabetes was treated over enthusiastically in the outside hospital and that the stupor was due to profound brain damage resulting from hypoglycemia? This point comes to my mind because as you will recall in the history this patient had never taken insulin prior to her admission to the outside hospital.

DR. ROBERT J. GLASER: When this patient entered the hospital, it was noted that two or three suggestive petechiae were present and examination of the heart revealed no murmurs. Subsequently, a very distinct systolic murmur of grade II intensity appeared. I wonder if she may not have developed acute bacterial endocarditis secondary to the coliform bacteremia. Since the patient's temperature was up throughout her hospital stay, development of the murmur could not be attributed to hyperpyrexia. An interval of two days is rather short for the development of such a murmur, even in acute bacterial endocarditis, but I think the diagnosis should be mentioned.

DR. ALEXANDER: I think your suggestion is a good one. The findings brought to my mind also the possibility of acute bacterial endocarditis. Dr. Smith, do you believe that this infection may have involved one of the valves?

DR. JOHN R. SMITH: I do not believe that the development of the murmur was too unusual in view of the extremely critical condition of the patient and the overwhelming infection, but I agree that the diagnosis of acute endocarditis must be considered.

DR. CYRIL M. MACBRYDE: I think that the comatose state was not due to uncontrolled diabetes but rather to severe infec-

[1] HARVEY, A. M. Salmonella suipestifer infections in human beings. *Arch. Int. Med.*, 59: 118, 1937.

tion. When the patient entered this hospital, her carbon dioxide combining power was essentially normal; the dehydration was corrected and the diabetes was well controlled. It must be kept in mind that occasional patients who develop severe diabetic coma remain in the coma and die even after correction of electrolyte abnormalities and control of hyperglycemia. I think hypoglycemia is quite a rare cause of death in this situation.

DR. ALEXANDER: How long may a patient survive in coma due to diabetic acidosis?

DR. MACBRYDE: Rarely over twenty-four hours if the situation is not corrected.

DR. HARFORD: One other point in regard to the effect of bacteremia on coma may be made. Poured plates, made from blood taken on admission and on the second hospital day, showed very large numbers of organisms, but on the last day of life although the blood culture was positive the poured plates showed only a few colonies. That final culture, which was taken after twenty-four hours of streptomycin treatment, indicated that the infection was coming under control, at least as far as the blood stream was concerned and one would expect that had the stupor been due to bacteremia it should have lessened.

DR. ALEXANDER: In summary, I think we all agree that this patient probably had severe renal infection, probably acute pyelonephritis, and that possibly her kidneys were also the seat of chronic changes, among which have been mentioned intercapillary glomerulosclerosis. Necrotizing renal papillitis has been suggested as an accompanying feature of the acute pyelonephritis and finally acute bacterial endocarditis has been mentioned.

Clinical Diagnoses: Acute pyelonephritis; ? necrotizing papillitis; ? intercapillary glomerulosclerosis; ? acute bacterial endocarditis due to colon bacillus.

PATHOLOGIC DISCUSSION

DR. VOL K. PHILLIPS: At autopsy the body was that of a well developed, fairly well nourished, middle-aged, white woman weighing 64 Kg. Externally there were no lesions.

The more significant findings were in the kidneys. The left kidney was greatly enlarged and weighed 440 Gm. The thin transparent capsule retracted from the cut edge and stripped easily to expose a pale red cortical surface, upon which there were numerous yellow, soft, slightly elevated foci from 1 to 4 mm. in diameter, some of which had tiny red centers. There were no scars or gross deformity. The parenchyma bulged from the cut surface and the pelvis was packed with thick, reddish-grey, purulent material. The wall of the pelvis was thickened and the mucosa was granular with numerous dilated, small blood vessels. The center of each pyramid contained a depressed, reddish-grey, firm focus, 12 to 20 mm. in diameter, surrounded by a slightly raised yellow border 1 to 2 mm. thick. Extending peripherally there were very dark purplish-red radiating lines which followed the distribution of the collecting tubules. In the inferior pole was an irregular cavity 24 by 12 by 10 mm. which was lined by a shaggy grey friable material; the cavity contained an irregular solid mass of a similarly friable substance 1 cm. in diameter. The inferior calyx led directly to this cavity which had completely replaced the renal papilla normally present in that location.

The right kidney was not as large as the left, weighing 250 Gm. It showed similar but less striking gross pathologic changes in the parenchyma, papillae and pelvis but there were neither abscesses nor completely destroyed papillae.

The urinary bladder contained a large amount of thick, reddish-grey purulent material. The mucosa was edematous and large bullae were present. Near the urethra there was a small, dark, red focus where the mucosa was inflamed and ulcerated. There was no anatomic obstruction of any part of the urinary tract.

There was clear fluid present in each pleural cavity, 500 cc. on the left and 300 cc.

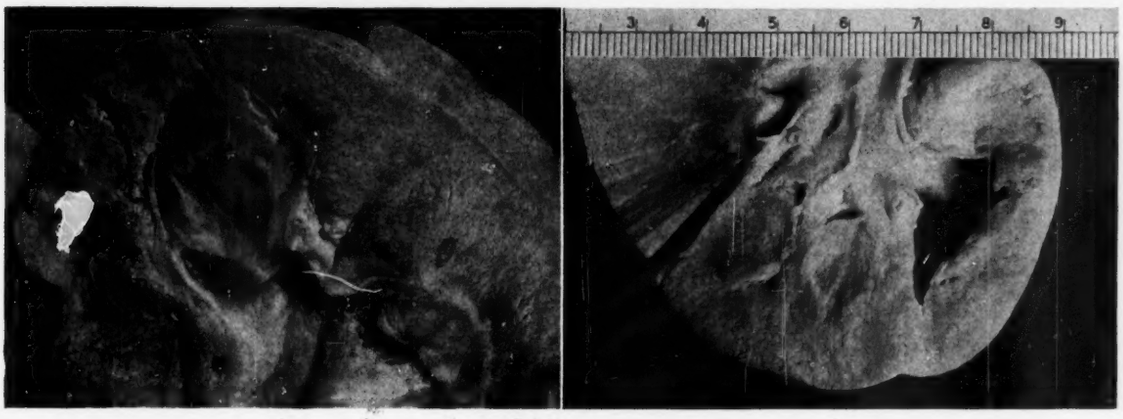

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FIG. 1. Gross appearance of necrotizing papillitis in the right kidney.
FIG. 2. Cavity in the lower pole of the right kidney which communicates directly with the pelvis and represents a totally destroyed renal pyramid.

on the right; in the peritoneal cavity 250 cc. of fluid were present. The serous membranes throughout the body were smooth and glistening. The liver was moderately enlarged, weighing 2,420 Gm., and was of a yellow, greasy appearance on the cut surface. The lungs and spleen were congested; the other viscera showed no pathologic lesions of major significance.

DR. ROBERT A. MOORE: We have not previously had the opportunity to present at one of these conferences a case with this highly characteristic renal lesion which occurs in association with diabetes and which is illustrated in the first two photographs of the left kidney. Figure 1 illustrates the typical lesion of necrotizing papillitis in which the central portion of a papilla is converted into grey-red tissue with linear striations which follow the normal architecture of that region of the kidney, indicating that the anatomic change had not progressed to the point where destruction of the architecture ensued. This central area is surrounded by a slightly elevated, yellow zone, varying from 1 to 2 mm. in thickness, beyond which are red streaks spreading into the surrounding pyramid. The second photograph (Fig. 2) is of the cavity in the lower pole of the kidney which at autopsy was partially filled with granular débris such as might have resulted from extension of the necrosis present in the other papillae and sloughing of the involved tissue.

Figure 3 is a slightly magnified microscopic section of a lesion similar to the one seen in Figure 1. Considered with Figure 4, which is a higher magnification of the irregular, dark line representing the narrow yellow peripheral zone seen grossly, it is apparent that the peripheral zone is a cellular region and the central zone is relatively free of cells. This lesion represents a combination of the pathologic changes which result from infection plus the occlusion of blood vessel changes leading to ischemic necrosis of tissue. In the cellular zone there is an intense inflammatory reaction with diffuse infiltration of polymorphonuclear leukocytes, many of which are undergoing necrosis themselves with karyorrhexis and karyolysis of the nuclei.

Figure 5 represents another lesion in the area of viable tissue in which there are small blood vessels filled with thrombi. These thrombi were probably produced as a result of the severe infection which seems to affect the pyramids primarily; the formation of such thrombi results in interruption of the blood supply to the entire tip of the renal pyramid. Beyond this zone there are tubules filled with polymorphonuclear leukocytes and small acute abscesses are seen in the parenchyma of the cortex.

This patient had, in addition, arteriolar disease of the kidney as is evidenced by the prominently thickened arteriole at the base of the glomerular tuft. (Fig. 6.) Although

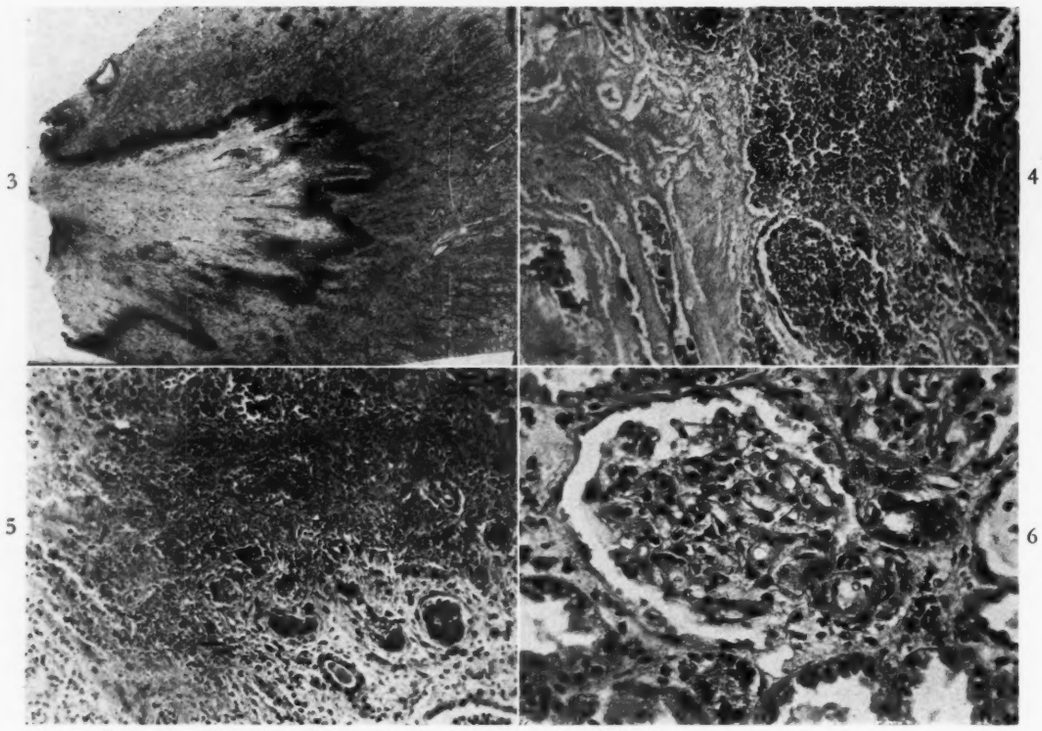


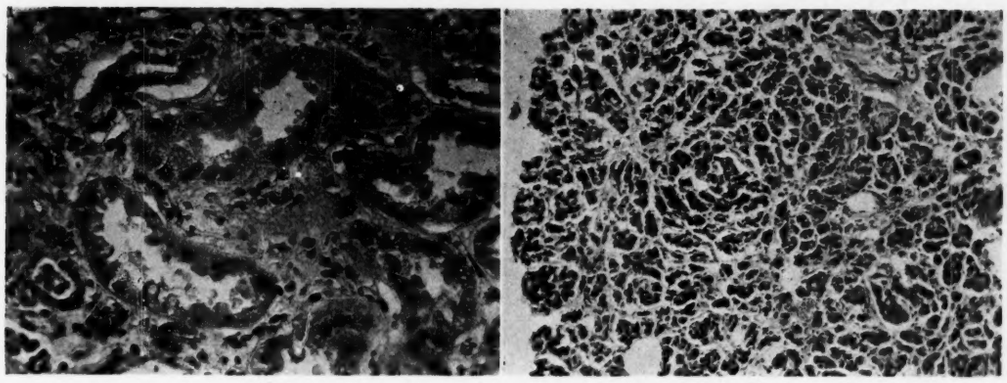
FIG. 3. Low magnification of an area of necrotizing papillitis.
FIG. 4. Moderate magnification of the edge of a necrotic papilla with the zone of ischemic necrosis to the left and the peripheral zone of cellular infiltration on the right.
FIG. 5. Peripheral zone of inflammation and thrombi in small blood vessels in an affected renal pyramid.
FIG. 6. Thickened afferent arteriole and slight thickening of the basement membrane of the capillaries in the kidney.

uremia is not an anatomic diagnosis, we may make observations at the time of autopsy which suggest the existence of nitrogen retention prior to death. This particular patient did not have inflammation of the serous cavities, especially pericarditis which is frequently found in uremia. Further, there was no observation at the time of autopsy that the material from the cecum had an ammoniacal odor, another of the very characteristic pathologic signs of uremia. Thickened arterioles, such as the one illustrated in Figure 6, contained foci of necrosis as though the lesions of malignant nephrosclerosis were either incipient or had just begun before death; I do not think, however, that the vascular changes had progressed as yet to the point where that diagnosis can be added.

Microscopic sections of the kidneys also showed a slight thickening of the glomerular basement membrane, again an indication of arteriolar disease. In addition, there were occasional small deposits in the glomeruli of the dense material characteristic of intercapillary glomerulosclerosis; although this patient did have intercapillary glomerulosclerosis, I doubt that that lesion had anything to do with the terminal episode. In our experience a slight degree of intercapillary glomerulosclerosis usually gives rise to no significant clinical signs or symptoms.[2]

The renal tubules showed a good deal of change. Figure 7 is a fairly typical example of the proximal convoluted tubules in the kidneys; you will note that there is a great variation in the staining properties of the nuclei. The finding suggests that there had been rather severe damage to the proximal convoluted tubular epithelium for a prolonged period of time; there are some regions where no nuclei remain whereas in

[2] GOODOF, I. I. Intercapillary glomerulosclerosis. *Ann. Int. Med.*, 22: 373, 1945.



7 8

FIG. 7. Proximal convoluted renal tubules with variable intensity of staining. There are some foci in which there has been loss of nuclei and others in which nuclei have accumulated, indicating beginning regeneration.
FIG. 8. Slight diffuse interstitial fibrosis in the pancreas.

others there is an accumulation of nuclei indicative of beginning regeneration.

The anatomic lesions in the pancreas which might be attributed to diabetes were not very striking. Figure 8 illustrates the fairly typical example of slight interstitial fibrosis which was present. The islets are for the most part fairly well preserved and only in a few areas are single hyaline islet cells seen. The arteriolar changes in the pancreas were striking; many vessels had walls which were about twice as thick as normal and completely hyalinized.

In summary, this patient had a very characteristic lesion which is seen in the kidney in some cases of diabetes. From the anatomic standpoint it is the result of a severe, rapidly progressing infection which produces occlusion of blood vessels and leads to the secondary changes of ischemic necrosis in the renal papillae. The lesion and its associations with diabetes has been emphasized in the literature, principally during the past few years, and the paper of Edmondson et al.[3] may be consulted for further study.

Anatomic Diagnoses: Acute pyelonephritis with abscess formation, left severe, right moderate; Escherichia coli cultured from the heart's blood and the renal pelves; necrotizing papillitis, left kidney severe, right moderate; acute cystitis; arteriolar nephrosclerosis; intercapillary glomerulosclerosis, slight; arteriosclerosis, generalized, slight.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University of Medicine.

[3] EDMONDSON, H. A., MARTIN, H. A. and EVANS, N. Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus. *Arch. Int. Med.*, 79: 148, 1947.

Case Reports

Acute Endocarditis Due to Staphylococcus Aureus Successfully Treated with Penicillin*

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The successful treatment of endocarditis due to Staphylococcus aureus with penicillin is still unusual as is evidenced by the fact that we were able to find only twelve such cases in the literature. These cases, as well as the one which we are reporting, are summarized in Table 1.

Table 1
RESUMÉ OF CASES REPORTED IN THE LITERATURE

Author	Daily Dose Penicillin x 1 Million Units	Route	Days Treated	Total Penicillin x 1 Million Units	Results
Dolphin[1]	0.048–0.12	IM	36	2.1	well, 12 mo.*†
Glaser[2]	0.36	IV	13	4.7	well, 21 mo.
Glaser	0.04–0.3	IV, IM	26	3.1	well, 20 mo.
Glaser	0.2–1.2	IM	22	11.6	well, 10 mo.
Glaser	0.24–1.2	IV, IM	67	58.6	well, 1½ mo.
Harford[3]	.....	IV, IM	13	4.9	well, 4 mo.*
Harford	.....	IV, IM	25	3.2	well, 2 mo.*
Harris[4]	0.045–0.4	IM	46	6.3	well, 7 mo.*†
Howells[5]	0.32	IM	9	3.0	well, 1 mo.*
Hoyt[6]	0.12	IM	14	1.7	well, 18 mo.*
MacNeal[7]	0.0072–0.12	IM	62	3.7	well, 11 mo.†‡
Wilhelm[8]	0.2–2.0	IM	56	13.4	well, 20 mo.*
Guest and Harrison	1.04	IV, IM	43	44.6	well, 32 mo.

IV, intravenously; IM intramuscularly.
* Sulfonamide also given.
† Penicillin given intermittently in three or more courses.
‡ Staph. aureus bacteriophage, thiobismol and neoarsphenamine also given.

CASE REPORT

H. B., a twenty-two year old white female, was admitted to the Bassett Hospital on December 9, 1945. At the age of fourteen she had had chorea and four years later a heart murmur was first noted. The present illness began abruptly fifteen days before admission, with fever of 102°F., malaise, chilly sensations, nausea, vomiting and diarrhea. In the course of the next four days the gastrointestinal symptoms largely subsided, to be replaced by coryza, sore throat and a cough productive of mucoid sputum. Her fever rose to 104°F. She was given penicillin, 15,000 units intramuscularly, every three hours for the next two days, but in spite of this her temperature continued at a high level, her shoulder joints became tender and painful and there was syncope on one occasion. Eight days before admission she entered another hospital where a tentative diagnosis of acute rheumatic fever was made, for which she received 4 to 6 Gm. of aspirin daily for the next four days. Four days before admission the patient became jaundiced and petechiae were

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noted on the toes and in the conjunctivae. A blood culture taken on this day was subsequently reported positive for a gram-positive coccal organism. On each of the last two days before admission she received an infusion containing 200,000 units of penicillin. Despite this she became confused and lethargic and her temperature rose to 105°F.

Physical examination on admission revealed that the temperature (rectal) was 101.2°F., pulse rate 60, respiratory rate 26, blood pressure 105/62 and weight 120 pounds. The patient appeared acutely ill, dyspneic and drowsy. The skin was hot, dry and icteric. There were petechiae on the conjunctivae, soft palate and left tonsillar fossa, a round retinal hemorrhage was present, and a tender, hemorrhagic lesion was visible on the fourth right toe. On the extremities there were scattered, dull red macules, 4 to 6 mm. in diameter, which blanched with pressure. There was a pustule on the left leg. The tip of the third right finger, pricked for a blood count before admission, appeared infected. Cardiac dullness extended just beyond the mid-clavicular line in the left fifth interspace. The rhythm was regular. There were loud apical and basal systolic murmurs as well as a blowing diastolic murmur along the left sternal border which was loudest in the third interspace. The spleen was palpable and tender. The lungs were clear, the liver was not enlarged, the neck veins were not engorged, there was no cyanosis, no dependent edema and no evidence of meningeal irritation.

Laboratory studies revealed the following: The hemoglobin was 11.3 Gm. and the white blood count was 9,000 with 84 per cent neutrophiles. The erythrocyte sedimentation rate (Wintrobe's method, uncorrected) was 49 mm. fall in one hour. The icterus index was 14. A blood culture was positive for Staphylococcus aureus hemolyticus, coagulase positive. The colony count was 227 per cc. of blood. A culture of the pustule on the left leg was positive for a similar organism. The micro-organism from the blood culture grew in a concentration of 0.06 units of penicillin per cc. and was inhibited by a concentration of 0.125 units (Kolmer's method). It was also inhibited by 10 mg. per cent of sulfathiazole. A catheterized urine specimen showed 1 plus albumin, 2 to 4 red blood cells per high power field, and from it Staphylococcus albus and coliform bacilli were cultured. An electrocardiogram was normal. A portable chest x-ray showed probable cardiac enlargement.

The course in the hospital (shown in the accompanying illustration) was stormy. On the second hospital day the patient became semi-comatose, her temperature rose to 106.6°F., the pulse rate to 130 and the respiratory rate to 50. There were many crackling râles at both lung bases and a gallop rhythm developed. A continuous infusion of penicillin, 800,000 units in each twenty-four-hour period, together with intramuscular injections of 80,000 units every eight hours, were started and continued for forty-three days. Oxygen was administered by nasal catheter for the first eight hospital days. The hemoglobin rose from a low of 9.9 to 14.7 Gm. after five small blood transfusions were given during the first hospital week. There was no subsequent anemia. Although the spiking fever and rapid pulse were slow in abating, the patient's appearance rapidly improved during the first ten days. She became mentally alert. Dyspnea, icterus and gallop rhythm disappeared. The spleen was not palpable at the end of the second hospital week. Nevertheless, a positive blood culture in three of five flasks was obtained on the fourteenth hospital day. Because of this and because the microorganism was moderately sensitive to sulfathiazole, this drug was given from the nineteenth to the sixtieth hospital days (total dosage was 234 Gm.). Intermittent microscopic hematuria continued until the twentieth hospital day. No peripheral embolic phenomena were noted from the twentieth to the thirty-second hospital day when an Osler's node appeared on the left hand. Two weeks later she was ambulatory and was discharged on the sixty-sixth hospital day.

An inconstant, soft, low pitched, apical diastolic murmur was heard during her hospitalization. The basal diastolic murmur became louder but the systolic murmurs decreased in intensity. Her blood pressure averaged about 110/75. After the first hospital week there were no signs of cardiac failure. X-rays showed a 15 per cent increase in the cardiac size (as estimated by the Ungerleider table). The cardiac silhouette was not diagnostic of any particular valvular lesion.

The patient has been followed for fifteen months and there has been no evidence of recurrence. Six blood cultures have been negative. The erythrocyte sedimentation rate has been within normal limits. The basal diastolic murmur has persisted unchanged but the basal

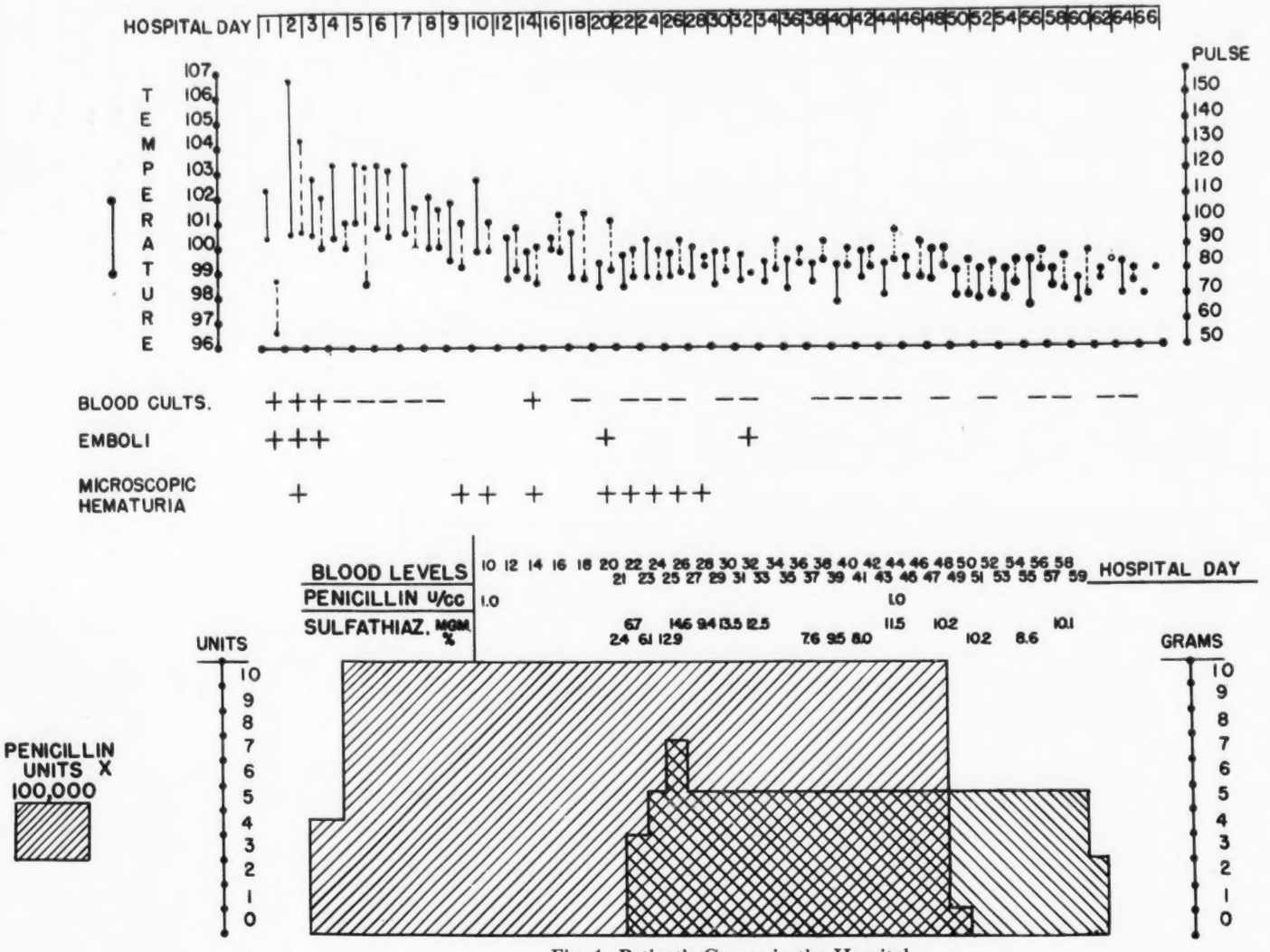

Fig. 1. Patient's Course in the Hospital.

systolic murmur has disappeared and the apical systolic murmur has become less pronounced. There has been no evidence of cardiac failure and the cardiac silhouette, as seen in x-ray examinations, has remained unchanged. Her activities were gradually increased and for the last eight months she has been able to carry on her duties as a school teacher.

COMMENT

The most notable feature of the available reports on the treatment of Staph. aureus endocarditis with penicillin is the low dosage as compared to present day practice. This may well be an important factor in the cause of the previous high mortality in penicillin-treated patients inasmuch as these patients are likely to die rapidly of overwhelming infection. To be sure one is usually dealing with an organism relatively sensitive to penicillin, yet our patient had one positive blood culture after receiving 12 million units of the drug, an amount greater than the total dosage of all but two of the previously reported cases. In our patient therapy was delayed for some hours in order to establish an accurate bacteriologic diagnosis. In retrospect we doubt that this delay was justifiable. We also believe that our dosage schedule, thought at the time to be high, should now be regarded as minimal.

SUMMARY

1. The previously reported cases of those with Staph. aureus endocarditis who were treated successfully with penicillin, together with one of our own, are tabulated.

2. Suggestions are made regarding the therapeutic approach to this disease.

ADDENDUM

On November 9, 1948, thirty-two months after discharge from the hospital, the patient's private physician informed me that she is married and well.

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A Case of Infectious Mononucleosis with Jaundice and Thrombocytopenic Purpura*

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The protean manifestations of infectious mononucleosis and the varied conditions which it may simulate are well known to all. Jaundice was only rarely encountered in infectious mononucleosis[1] until World War II.[2] In contrast to the many reports of jaundice complicating infectious mononucleosis in military personnel during the war no cases of thrombocytopenic purpura were mentioned.[3] To date very few such cases can be found in the literature.[4–6] Because of the rarity of the combination of thrombocytopenic purpura and jaundice as complicating conditions in infectious mononucleosis, and to stress the fact that the presence of mild jaundice indicates the benign character of purpura hemorrhagica, the following case is considered worthy of report.

CASE REPORT

R. H., a white male aged twenty-one, was admitted to Beth Israel Hospital on February 28, 1946. The past history was irrelevant. A week before admission the patient was seized with general malaise and a "grippy" feeling. At the onset the temperature was 103°F. The fever declined rapidly but two days later severe headache, anorexia and vomiting developed. The day before admission the patient noticed that his stools were clay-colored. On the morning of admission he awoke from sleep with marked bleeding from the gums, epistaxis and hematemesis. He also noticed large ecchymotic areas and smaller purpuric spots on both thighs.

Table I
URINARY FINDINGS

Date	Albumin	Bile	Urobilin	Urobilinogen	R.B.C.
February 28	Trace	+	..	..	90–100
March 1	.....	+	..	+	.....
March 2	.....	+	..	+	.....
March 3	.....	0	..	..	2–3

Upon first examination the patient was found to be mildly jaundiced. This was overshadowed by the predominant clinical finding of hemorrhagic diathesis such as marked epistaxis, requiring packing of the nose, and excessive bleeding from soft, spongy gums. Upon taking the blood pressure diffuse areas of purpura (Rumpel-Leede phenomenon) were produced. No glands were palpable nor could the spleen be felt. The blood pressure was 110 systolic and 70 diastolic. The pulse was 63. The clinical picture the first day of admission resembled acute leukemia or thrombocytopenic purpura. The urine showed a trace of albumin; 1 plus bile and urobilinogen and 90 to 100 red blood cells which gradually returned to normal. (Table I.)

The peripheral blood findings are tabulated in Table II. It is seen that there was no anemia, the hemoglobin and red blood cells being normal. There was a tendency to leukopenia with a shift to the left. The increased and abnormal lymphocytes were of the type most commonly seen in acute infectious mononucleosis. The platelets

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were considerably diminished. A bone marrow study showed no abnormality. (Table III.) Megakaryocytes were present in low, normal numbers and not greatly increased as in the usual case of idiopathic thrombocytopenic purpura. This low megakaryocyte level suggested some defect in fragmentation of the platelets connected with an unusual reaction of the bone marrow which would diminish as the infection cleared up.

In addition to the purpura hemorrhagica, hepatitis was undoubtedly present as shown by the jaundice, direct van den Bergh reaction, a positive Hanger cephalin flocculation test and low cholesterol and cholesterol esters. (Table IV.)

During the patient's stay in the hospital (ten days) the temperature was not elevated and there was a gradual recession of the purpura and icterus.

TABLE II

PERIPHERAL BLOOD FINDINGS

Date	R.B.C. (million)	Hemoglobin %	Hemoglobin Gm.	W.B.C.	Bands	Segments	Basophiles	Eosinophiles	Lymphocytes	Monocytes	Platelets
February 28	5.10	97	15	7,800	19	22	..	..	50	9	
March 1	4.98	101	17	4,800	6	37	1	3	37	6	30,600
March 2	5.00	91	14	7,500	5	61	..	1	24	7	35,000
March 5	4.56	91	14	7,250	6	57	1	3	30	5	296,400
March 10	5.25	103	18	8,350	4	46	..	5	45	0	
October 1	4.10	92	15	8,000	..	60	..	1	32	7	

TABLE III

STERNAL BONE MARROW PUNCTURE

Nucleated cells, 35,000
Megakaryocytes, 22
Myeloblasts, 2 per cent
Promyelocytes, neutrophiles, 4 per cent
Myelocytes, neutrophiles, 39 per cent
Eosinophiles, 1 per cent
Non-segmented polymorphonuclears, 16 per cent
Segmented polymorphonuclears, 3 per cent
Segmented polymorphonuclear eosinophiles, 1 per cent
Plasma cells, 2 per cent
Hematogones, 3 per cent
Lymphocytes, 10 per cent
Erythroblasts, 5 per cent
Normoblasts, 14 per cent

COMMENT

In view of the onset with diffuse bleeding the possibility of acute leukemia had to be considered. This was ruled out by the absence of enlarged lymph nodes, spleen, or leukemic cells in the bone marrow. The normal bone marrow also ruled out true thrombocytopenic purpura. The diagnostic problem in this case was to correlate the three outstanding clinical findings: jaundice, purpura and the peripheral blood picture of infectious mononucleosis. Were we deal-

TABLE IV

LIVER FUNCTION STUDIES

Date	Icteric Index	van den Bergh	Bilirubin (mg. %)	Serum Protein (Gm. %)	Albumin (Gm. %)	Globulin (Gm. %)	Cholesterol (Mg. %)	Cholesterol (Mg. %)	Cephalin Flocculation Test (24–48 hr.)	
March 1	27.6	direct prompt	6.1	...	...	...	114	..	+++	++++
March 6	25.6	.....	...	5.7	3.9	1.8				
March 8	12.5	.....	...	...	...	...	138	40		
March 10	10.1	.....	...	6.7	5.1	1.6	...	..	0	+
October 1	....	.....	...	...	...	...	...	..	0	0

ing with infectious mononucleosis complicated by hepatitis and thrombocytopenic purpura or with infectious hepatitis with the blood picture of leukopenia, mononucleosis, lymphocytosis and the added complication of thrombocytopenic purpura?

As illustrated in the case the differentiation between infectious hepatitis and infectious mononucleosis complicated by jaundice is often difficult. The mechanism of the production of jaundice in cases of infectious mononucleosis is not definitely established yet. There are two schools of thought: one believes that the jaundice is due to enlarged lymph nodes pressing mechanically on the bile ducts;[11] the newer belief is that it is a direct toxic action upon the liver itself.[12]

TABLE V
BLOOD STUDIES

Date	Coagulation Time	Bleeding Time	Sedimentation Rate (mm.)	Prothrombin Times		Heterophile Reaction
				Whole (Sec.)	Dilute (Sec.)	
March 1	3′50″	10′30″	..	.....	.....	0
March 6	2′30″	3′50″	12	16.85	35.85	..
March 10	.....	.....	3	.....	.....	0

If purpura were not present in this case, the clinical picture would be more that of infectious hepatitis than of infectious mononucleosis. The onset of the disease with general malaise and grippy sensation is quite characteristic of hepatitis as well as the degree of jaundice and signs of liver damage. The blood picture of leukopenia, mononucleosis and lymphocytosis suggested the diagnosis of infectious mononucleosis. It should be noted, however, that this same blood picture may also be seen in the early stages of infectious hepatitis as recently demonstrated by Havens and Marck[8] in experimentally produced virus hepatitis in human volunteers. The absence of a positive Paul-Bunnell heterophile reaction does not preclude the diagnosis of infectious mononucleosis as reported by several investigators.[9,10]

Purpura is not encountered in infectious hepatitis except in a severely toxic case or one of acute yellow atrophy. In infectious mononucleosis, however, although thrombocytopenic purpura is an extremely rare complication, it does occur but is not of serious prognostic import, being seen even in milder cases. Considering the short duration of the bleeding diathesis in this patient, we believe the most suitable diagnosis is acute infectious mononucleosis with complicating hepatitis and thrombocytopenic purpura.

As for the production of purpura in infectious mononucleosis, Dameshek and Grassi[13] believe that it is due to a state of hypersplenism in which the spleen not only depresses the formation and delivery of megakaryocytes and platelets but causes a reduced delivery of neutrophiles from the bone marrow and thus results in lymphocytosis. Lloyd[4] believes it is the vascular damage secondary to acute infection together with a loss of circulating platelets at the purpuric site that causes the hemorrhagic phenomena. The low platelet count in the circulating blood may be the expression of a transient toxic effect exerted peripherally rather than centrally.

SUMMARY

A case of infectious mononucleosis with complicating jaundice and thrombocytopenic purpura is presented because of its rarity. The hemorrhagic phenomena of epistaxis, hematemesis, bleeding gums and petechiae simulated true thrombocytopenic purpura. However, the presence of a blood picture typical of infectious mononucleosis indicated a favorable prognosis which was

vindicated by the short duration of the hemorrhagic diathesis. The mechanisms of the production of the jaundice and thrombocytopenic purpura in infectious mononucleosis are discussed.

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Thrombophlebitis Migrans with Involvement of Both Lateral Sinuses

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ALTHOUGH lateral sinus thrombosis is not an uncommon complication of mastoid infection, instances of bilateral thrombosis are rare. Rarer still are lateral sinus thromboses of non-otitic origin. No parallel could be found in the literature to the case herein described of benign bilateral thrombosis from thrombophlebitis migrans.

CASE REPORT

J. B., a Jewish lawyer aged twenty-nine, was referred to the Sixth General Hospital by his physician, with the complaint of progressive loss of vision. He was first seen in mid-December, 1943. Loss of vision began insidiously seven months before and was accompanied at first by a moderately severe vertical headache. The headache subsided spontaneously in a few months but the loss of vision continued.

The patient was suspected of having a brain tumor because in addition to these complaints he was found to have papilledema, optic atrophy and a very high cerebrospinal fluid pressure.

The only element of note in the past history was the presence of migratory phlebitis of the lower extremities during the preceding seven years. A small segment of vein would become reddened, firm, somewhat tender and then subside to a painless area of induration. No treatment had been of avail and gradually all the veins of the legs and part of the thighs had become involved. Recently there had been an extension of the process to the upper extremities, neck and head.

Upon physical examination the patient was a slender, swarthy, well nourished man. There was chronic, non-pitting, woody edema from the ankles to the knees, with a mottled bluish discoloration of the overlying skin. No ulcerations or scars were noted. The temperature and arterial pulsations of the extremities were normal. A portion of the right frontal and angular veins was firm, cylindric, non-collapsible and reddened but non-tender. The left external jugular vein was similarly thrombosed through the upper half of its course. The lower portion could be distended by supraclavicular pressure and collapsed by its release.

The temperature, respirations, pulse rate and blood pressure were normal. Examination of the heart, lungs, abdomen and lymph nodes showed no abnormalities.

Neurologic examination was entirely negative except for the eyegrounds. The detailed report has been unfortunately lost in military transit but it is recalled that the visual acuity was approximately 20/70 in each eye, and perimetry revealed enlargement of the blind spots. There was about 1 diopter elevation of the right optic disc and somewhat less of the left. Both were very pale, although not chalk-white, and the margins were blurred. Engorgement of the veins and one or two resorbing hemorrhages were noted. The findings were considered typical of secondary optic atrophy from chronic papilledema.

Complete hematologic, urine and stool studies were done, with only a single abnormality noted: a persistent eosinophilia of 6 to 8 per cent. The Kahn test was negative as were repeated searches for parasites in the blood, urine and stools. The patient was even examined after 10 P.M. on one occasion for microfilariae. Inasmuch as most Moroccans and, indeed, most American soldiers in Morocco showed a similar degree of eosinophilia in routine laboratory investigations without any discoverable trace of parasitism, this finding was discounted. The absence of pain and the duration of symptoms were inconsistent with trichiniasis. Repeated blood cultures on routine and special media were negative.

On December 31, 1943, the patient appeared with a fresh 2 cm. area of reddening and swelling on the radial aspect of the right wrist. A portion

of the nodule was excised and fixed. Histologic examination showed a section of vein containing a completely occluding adherent thrombus. Mild inflammatory changes were found in the vein wall and adventitia.

Roentgenograms of the skull and chest were within normal limits. Cerebrospinal fluid was examined on two occasions and found to be entirely normal as to cytology, chemical components and the Wassermann test. The sole abnormality, confirming the referring physician, was a pressure each time in excess of 700 mm. of water and a positive Tobey-Ayer test[1] on either side.

A brain tumor was considered unlikely in view of complete absence of localizing signs, normal spinal fluid protein, spontaneous subsidence of the headache and negative skull films. On the other hand, a unitary diagnosis was suggested by the cephalic involvement with thrombophlebitis migrans and the bilaterally positive Tobey-Ayer test: extension of the thrombophlebitis into both lateral sinuses with consequent hydrocephalus and papilledema.

The patient was placed on full doses of sulfadiazine (4 Gm. initially and 1 Gm. every four hours) for a period of two weeks. No change in his condition was noted. Penicillin was not available.

A recent letter from his physician (three and one-half years later) states that the patient is well but gives no details.

COMMENTS

Frequency of Bilateral Thrombosis of Lateral Sinuses. Prior to this report only fifteen other cases of bilateral thrombosis of the lateral sinuses could be found recorded in the literature. The last complete review is that of Smith[2] in 1939. He collected ten cases from other reports and added one of his own. All were of otitic origin and all the patients recovered. Three were treated by ligation of both internal jugular veins and seven with ligation of only one. One recovered without ligation. Irish,[3] in a study of 12,000 consecutive necropsies, found three cases, two otitic and one from a posterior neck abscess. One case was added by Brownell[4] and one by Brown and Bowman.[5] Both were otitic and both patients died.

The writer has reviewed 12,000 consecutive necropsies at the Massachusetts General Hospital and found four more. Two were otitic, a third was an unsuspected finding in a sixty-five year old man dying of bronchopneumonia and pontine softening and the fourth occurred together with meningitis following removal of a melanotic sarcoma of the neck. This brings the total to twenty cases. The fact that nine of the twenty patients succumbed points to the seriousness of this complication. There is reason to believe that the condition occurs more commonly than the figures indicate. Authors tend to report only the cases that recover. Careful search of any large autopsy series should turn up a few instances. Even the autopsy figures are not correct for pathologists do not routinely examine the skull.

Clinical Effects of Bilateral Sinus Occlusion. Hastings[6] discusses bilateral internal jugular vein ligation in such conditions as tuberculous lymphadenitis, cancer of the pharynx and metastatic carcinoma. Among the effects noted were convulsive seizures, marked cyanosis and no effect. In Smith's[2] case bilateral thrombosis with ligation of one jugular vein was associated with papilledema and a cerebrospinal fluid pressure of 460 mm. of water. The patient was well after three years.

The Nature of Phlebitis (or Thrombophlebitis) Migrans. This condition is described under both these names. Thrombophlebitis is more accurately descriptive and the other name should be dropped. Homans[7] describes it as a true disease of the vein wall, occasionally in individuals with normal clotting tendency. It occupies a short length of vein wall, usually on an extremity. There is little tendency to embolism (this statement is denied by other authors.) Attempts have been made to link thrombophlebitis migrans to Buerger's disease (Thromboangiitis obliterans).[8] Swirsky and Cassano[9] describe it as an uncommon condition of unknown etiology involving chiefly the superficial veins of the extremities. Visceral organs are rarely involved. The course is variable and

usually benign. Up to 1943 there were only about one hundred reported cases with five acceptable autopsies.

Collateral Circulation. According to Gray's Anatomy[10] the following are the main anastomotic connections through which the great sinuses may drain into the systemic venous system when both lateral sinuses are occluded: (1) pterygoid plexus (via middle meningeals and cavernous sinuses); (2) occipital vein (via the parietal emissary vein); (3) inferior petrosal sinus (joins superior bulb of internal jugular and is blocked when internal jugular is ligated or thrombus extends down to the bulb); (4) pharyngeal veins (via posterior meningeals); (5) vertebral vein (via vein of the condyloid canal, internal vertebral venous plexuses and occipital and basilar sinuses); (6) diploic veins (via meningeal and pericranial connections); (7) the ophthalmic veins; (8) nine groups of emissary veins some of which were first mentioned. There are many accessory connections.

SUMMARY

An instance of thrombophlebitis migrans verified by histologic study is presented.

The patient suffered thrombosis of both lateral sinuses from cephalic extension of the disease, a complication previously unreported. He recovered.

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AUTHOR INDEX VOLUME V

SUBJECT INDEX VOLUME V

(E.) = Editorial

The American Journal of Medicine

Volume V

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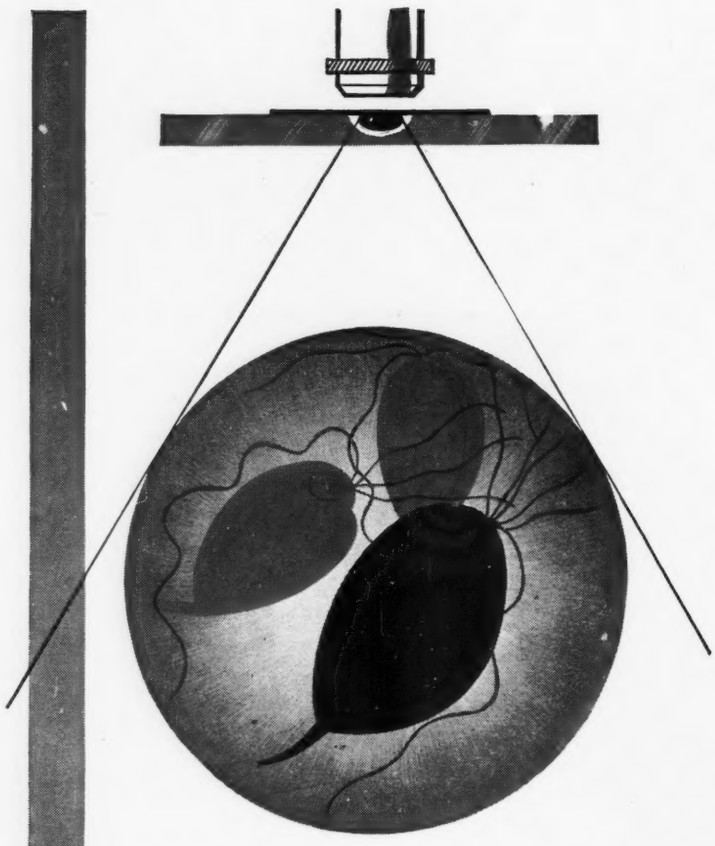

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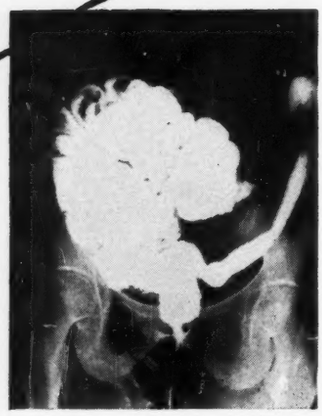

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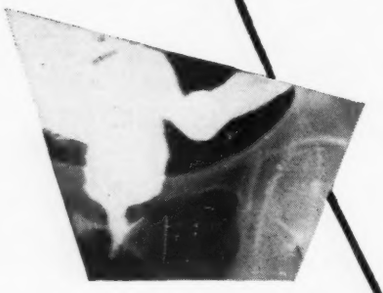

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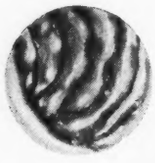

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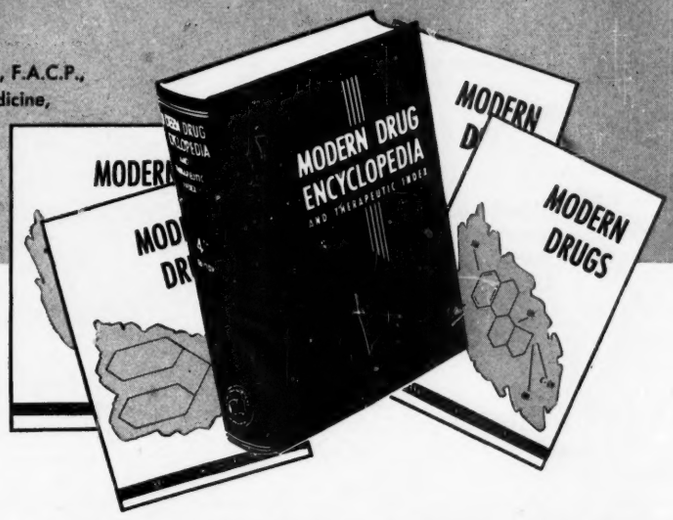

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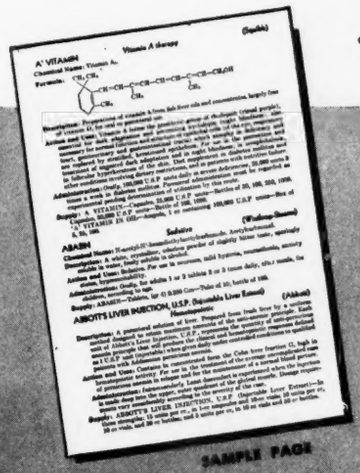
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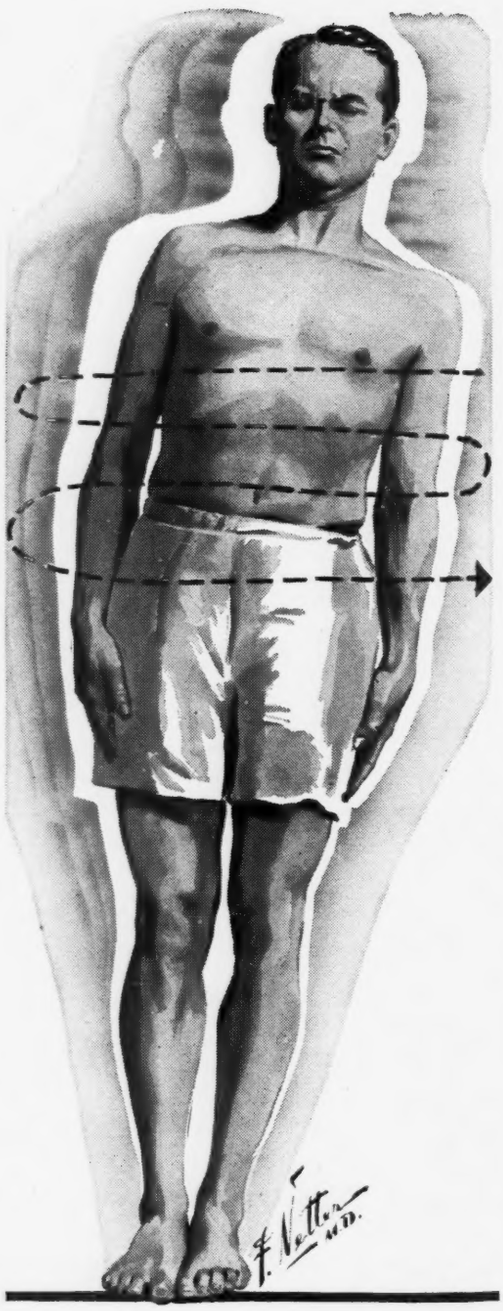

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